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REVIEW

Management of acute carbamazepine poisoning: A narrative review

Luan Wang, Yang Wang, Ruo-Ying Zhang, Yao Wang, Wei Liang, Tie-Gang Li

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Abstract

Standard management protocols are lacking and specific antidotes are unavailable for acute carbamazepine (CBZ) poisoning. The objective of this review is to provide currently available information on acute CBZ poisoning, including its management, by describing and summarizing various therapeutic methods for its treatment according to previously published studies. Several treatment methods for CBZ poisoning will be briefly introduced, their advantages and disadvantages will be analyzed and compared, and suggestions for the clinical treatment of CBZ poisoning will be provided. A literature search was performed in various English and Chinese databases. In addition, the reference lists of identified articles were screened for additional relevant studies, including non-indexed reports. Non-peer-reviewed sources were also included. In the present review, 154 articles met the inclusion criteria including case reports, case series, descriptive cohorts, pharmacokinetic studies, and *in vitro* studies. Data on 67 patients, including 4 fatalities, were reviewed. Based on the summary of cases reported in the included articles, the cure rate of CBZ poisoning after symptomatic treatment was 82% and the efficiency of hemoperfusion was 58.2%. Based on the literature review, CBZ is moderately dialyzable and the recommendation for CBZ poisoning is supportive management and gastric lavage. In severe cases, extracorporeal treatment is recommended, with hemodialysis as the first choice.

Key Words: Carbamazepine poisoning; Management; Activated charcoal therapy; Extracorporeal treatment; Intravenous lipid emulsion

Core Tip: There is no effective Antidote and standard treatment management for carbamazepine (CBZ) poisoning. This paper describes and summarizes the detailed clinical evidence of the treatment and management of CBZ poisoning, including gastric lavage and activated carbon therapy, hemoplavage, hemodialysis, continuous renal replacement treatment and plasmapheresis. Finally, this paper also provides the lipid resuscitation therapy to provide help for clinical treatment. In general, this paper summarized the results of CBZ poisoning related research, and provided the best plan for CBZ poisoning treatment.

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INTRODUCTION

Carbamazepine (CBZ) was discovered by Walter Schindler in 1953 and first utilized to treat partial tonic-clonic seizures in the United States in 1974[1]. Currently, CBZ is widely used for the treatment of epilepsy and peripheral neuralgia. Broad indications for the use and widespread availability of CBZ increase the risk of overdose, and CBZ intoxication accounts for a large proportion of life-threatening cases of anticonvulsant toxicity[2-4]. A systematic review of CBZ was published in 2014 by the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup that provides recommendations for the use of extracorporeal treatments (ECTRs) in cases of CBZ poisoning[5]. Currently, standard management protocols are lacking and specific antidotes for acute CBZ poisoning are unavailable; thus, we reviewed and summarized the various therapeutic methods for the treatment of CBZ poisoning described in previous studies. Our goal was to provide currently available information on acute CBZ poisoning, including its management. We believe this paper will help clinicians effectively manage patients suffering from CBZ intoxication.

METHODOLOGY

A literature search was performed in the following databases: PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Wanfang. The search strategy, in English and Chinese, used the terms "acute" and "carbamazepine" in combination with the keywords "poisoning", "intoxication", "toxication", "toxicity", "overdose", and "overdosage". These search terms identified 861 records. In addition, the reference lists of the identified articles were screened for additional relevant studies, and these additional searches added three records. Non-peer-reviewed sources were also searched, including books and Internet resources, which yielded 10 records. A total of 874 records were found, which were screened based on title, author, journal name, and publication date for repeatability and relevance. We excluded papers that were duplicates, non-English or non-Chinese papers, letters to editors, and those not referring specifically to the mechanisms of action, clinical features, and management of CBZ toxicity in humans. Finally, 154 articles were considered eligible for review. The majority of papers were case reports or small case series. The literature selection process is described in Figure 1.

PHARMACOLOGY

CBZ is an iminostilbene derivative that is structurally similar to tricyclic antidepressants and is mainly used as a potent first-line agent to treat epilepsy, including simple partial, complex partial, and general tonic-clonic seizures[6,7]. The therapeutic effects of CBZ have also been proven for the treatment of neuropathic pain, especially prosopalgia, central diabetes insipidus, attention-deficit/hyperactivity disorder, and bipolar disorder. CBZ is thought to exert its anticonvulsant effects by blocking presynaptic voltage-gated sodium channels in the central nervous system (CNS), which further prevents the release of glutamate and similar neurotransmitters, ultimately inhibiting high-frequency epileptic foci.

CBZ has a molecular weight of 236 Da and high protein binding affinity (70%-80%) for both albumin and alpha-1-acid glycoprotein. This percentage does not markedly decline, even in cases of overdose[8]. CBZ is highly lipophilic, a property that allows it to be rapidly distributed after ingestion with a moderately large volume of distribution ranging between 0.8 L/kg and 1.4 L/kg. Thus, at therapeutic doses, the immediate-release tablets and controlled-release formulation of CBZ have peak serum concentrations at approximately 6-8 h and 12-24 h post-ingestion, respectively[9-11]. However, following overdose, peak concentrations may be delayed up to 106 h[12] due to the anticholinergic properties of CBZ, which are responsible for decreased gastrointestinal (GI) motility and delayed and prolonged absorption[10,13].

CBZ metabolism predominantly and extensively occurs in the liver by epoxidation and hydroxylation reactions through the cytochrome P450 system. Only 1%–3% of the drug is not metabolized and excreted through the kidney. CBZ-

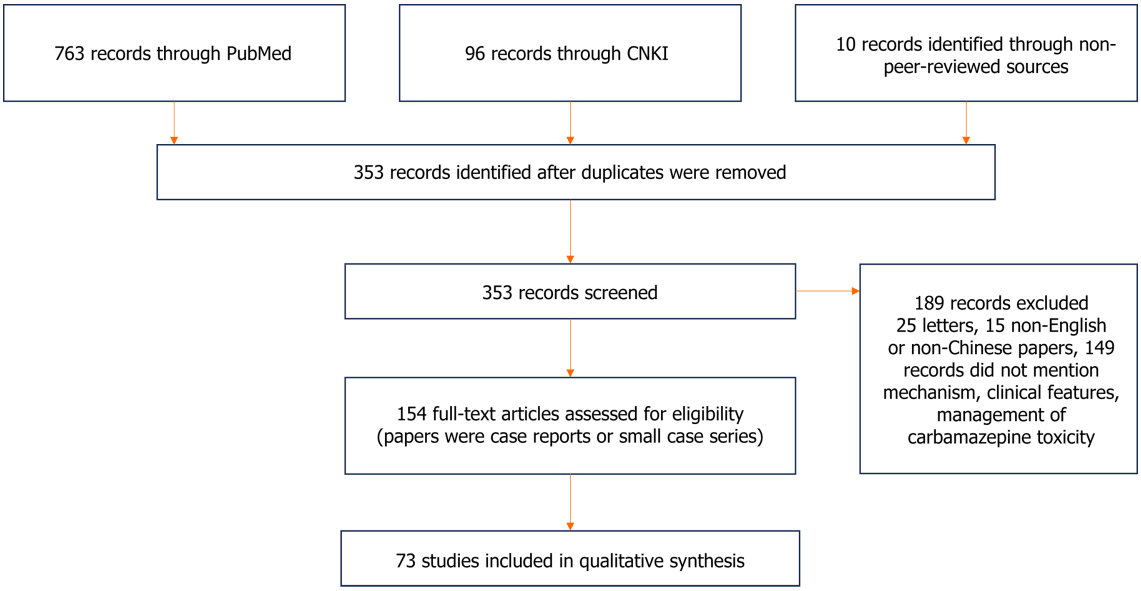

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Figure 1 Flow diagram of the literature search.

10,11-epoxide is the primary active metabolite and equally produces antiepileptic and toxic effects based on its capacity to form covalent protein conjugates[14,15]. CBZ-10,11-epoxide blood concentrations vary substantially between individuals, ranging from 15% to 55% of CBZ levels in adults and from 5% to 81% of CBZ levels in children[11]. CBZ metabolism is complicated because both normal metabolism and autoinduction of metabolism occur with chronic use.

There is wide interindividual variability in the pharmacokinetics of CBZ, as well as general adaptation[16]. CBZ is eliminated according to zero-order kinetics (*i.e.* a constant amount of drug is eliminated per unit time) in the case of elevated plasma drug levels, as seen in overdose; however, a delay in CBZ elimination occurs when no intervention is available[16]. The reported biological half-life of the initial dose of CBZ is 25-65 h, but is shortened to 12-17 h in chronically treated epileptic patients due to self-induction[17]. Nevertheless, the half-life is apparently much longer after excessive dosing and the use of controlled-release preparations[1,12], likely reflecting delayed or continuous absorption, impaired elimination, or a combination of both.

OVERVIEW OF CBZ POISONING

Toxicity from CBZ overdose was first described by Guntelberg in 1967[18]. CBZ intoxication increasingly accounts for a large proportion of life-threatening cases among anticonvulsant poisonings[2,3]. A total of 3734 toxic exposures to CBZ were reported in 2014 by the American Association of Poison Control Centers. Of these, 1880 were isolated ingestions. There were no deaths, but 62 cases were life-threatening or severely disabling due to the significant toxicity[19].

Although the toxic concentration of CBZ in patients is not completely consistent with clinical manifestations of toxicity, doctors often initially treat patients based on the patient's clinical status. However, serum CBZ concentration is a practical method used to confirm clinical exposure, and severe intoxication occurs at serum levels > 20 mg/L [therapeutic index range: 4-12 mg/L (17-51 μmol/L)][20]. Serum CBZ levels > 40 mg/L are generally predictive of severe toxicity[21], which potentially occurs at a lower concentration[22], especially in children[23-25], and tends to be associated with an increased risk of seizure, coma, respiratory depression, and cardiotoxicity[26,27]. In addition, the pharmacologically active metabolite of CBZ, CBZ-10,11-epoxide, contributes to the risk of toxicity[28,29]. Based on the circulating level of CBZ in blood, the effects of CBZ on the CNS can be classified into four stages: (1) Seizures and coma at levels > 25 mg/L; (2) Combativeness, hallucinations, and choreiform movements at levels of 15-25 mg/L; (3) Disorientation, drowsiness, and ataxia at levels of 11-15 mg/L; and (4) Potentially catastrophic relapse at levels < 11 mg/L[30]. The duration and severity of these stages are variable and depend upon the magnitude of the overdose[31]. The detailed clinical symptoms corresponding to the toxic dose are described in Figure 2.

Toxicity usually occurs within 1-3 h after ingestion, but may be prolonged due to the delayed and erratic absorption of CBZ[32,33]. A wide diversity of clinical manifestations such as neurologic, respiratory, and cardiac findings can be seen in CBZ poisoning[22,34]. CBZ intoxication primarily manifests as CNS symptoms including nystagmus, movement disorders, disturbance of consciousness, altered mental status ranging from drowsiness to coma, and convulsions[35-39]. Seizures are not uncommon, occurring in 11%-18% of overdose cases[40,41]. Respiratory depression, a common manifestation of severe overdose, may delineate the severity of toxicity in the respiratory system and may be complicated by concomitant aspiration. Myocardial depression, sinus tachycardia, hemodynamic instability hypotension, and cardiac conduction disturbances are characteristics of CBZ cardiotoxicity. Some rare electrocardiogram (ECG) abnormalities may also occur such as atrioventricular block, QRS interval prolongation, QTc (corrected QT time in ECG) prolongation (> 420

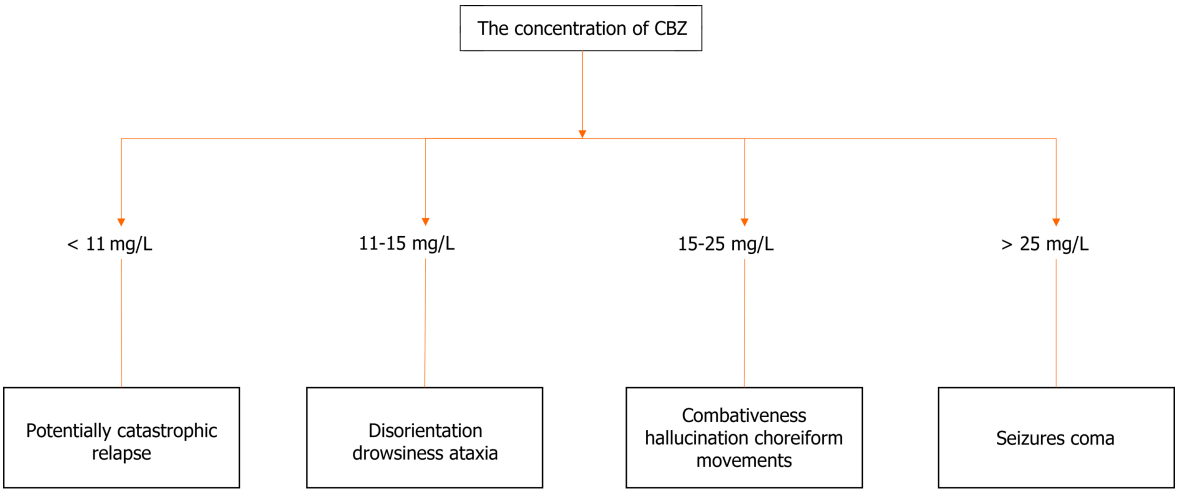

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Figure 2 Toxic dose and clinical manifestations of carbamazepine according to blood concentration. CBZ: Carbamazepine.

ms), bundle branch block, Brugada-type patterns, and premature ventricular contractions[42,43]. Death, though very uncommon (approximately 2% of cases), generally results from cardiovascular toxicity[44,45]. An overall mortality rate of 13% was documented and reported in a cohort study of 427 patients with CBZ intoxication, with an average CBZ intake in lethal cases of 23.6 g[22]. Refractory cardiovascular toxicity has also been reported[46,47].

MANAGEMENT OF ACUTE POISONING

In clinical practice, doctors initially treat patients based on their clinical symptoms, and supportive care plays a key role at this stage. For example, seizures are treated with benzodiazepines[48], hypotension is treated with vasopressors, and endotracheal intubation is used for patients with respiratory insufficiency. GI decontamination techniques such as gastric lavage (GL) and single-dose activated charcoal (AC) (SDAC) can be applied if patients are administered care within 1-2 h after ingestion without contraindications[49]. However, CBZ metabolism and distribution are complicated, and specific life-saving antidotes for CBZ poisoning are unavailable. Several modalities have been proposed to enhance CBZ clearance in patients with severe or life-threatening ingestion, including multiple-dose AC (MDAC), ECTRs, and lipid resuscitation therapy (LRT)[50].

Supportive care

Application of appropriate supportive care is adequate to deal with the vast majority of CBZ intoxication cases. Supportive care may involve airway protection with endotracheal intubation, treatment of seizures with benzodiazepines, and correction of hypotension with fluid challenges and vasopressors, if needed. The use of hypertonic sodium bicarbonate is indicated if ECG findings (QRS duration exceeding 100 msec) show that the sodium channel is blocked.

Serum CBZ concentrations in an acute overdose should be monitored serially (typically every 4-6 h) until a definitive downward trend is observed and the patient is improving clinically[51,52]. Continuous monitoring of serum CBZ concentrations in patients is necessary, especially in those with severe poisoning. These patients are likely to deteriorate after the initial improvement of clinical symptoms or develop a delayed toxic reaction due to a rebound effect (*i.e.* sudden rise in serum drug concentration following intermittent treatment due to drug redistribution from tissue to serum[53]) or sustained increase in serum concentration.

Patients with significant CNS depression may lose protective airway reflexes and should be intubated, particularly due to their lower seizure threshold. Short-acting neuromuscular blocking agents (*e.g.*, succinylcholine) are preferable so subsequent seizure activity is not masked. Induction agents with gamma-amino butyric acid agonist activity (*e.g.*, midazolam) may be preferable, depending on the patient's hemodynamic status.

Hypotension is initially treated with isotonic crystalloid. Caution should be exercised in patients at risk of volume overload, such as those with underlying heart disease or CBZ-induced myocardial dysfunction. Direct-acting vasopressors are used if intravenous fluids fail to correct the hypotension.

Sodium channel blockade may cause QRS interval prolongation, which, in other poisonings, has been shown to predispose patients to ventricular arrhythmias[54,55]. QRS prolongation due to CBZ toxicity is treated with sodium bicarbonate. Currently, there are no clearly established treatment thresholds based on QRS duration or dosing guidelines or evidence regarding the preferred method of administering sodium bicarbonate with respect to boluses, infusions, or treatment duration[56]. The proposed methods of administration are for patients with QRS intervals longer than 110 ms, particularly those with hypotension, and include boluses of a 1 mEq per 1 mL (8.4%) solution at a quantity of 1-2 mEq/kg to obtain a serum pH of 7.45-7.55 and an infusion of 150 mEq mixed with 1 L of 5% dextrose in water at a rate to maintain

that pH[54]. Continuous cardiac monitoring of patients with a 12-lead ECG is simultaneously needed. Volume overload, hypokalemia, hypernatremia, and metabolic alkalosis may result from prolonged bicarbonate infusions, and clinical and laboratory parameters must be closely followed to avoid these complications.

GL

GL has been routinely used to manage cases of poisoning for more than 200 years. However, GL carries significant risks, which, given its questionable clinical benefit, usually outweigh arguments in favor of its use; thus, it is not recommended for routine GI decontamination[57]. GL works by eliminating poison remaining in the GI tract and should be considered based on the time elapsed from oral ingestion to admission to the emergency department. In cases of suspected CBZ intoxication, prior to the determination of the current plasma concentration of CBZ, it is imperative to remove undigested tablets through GL to further reduce GI absorption. This one simple measure may be particularly helpful for CBZ intoxication given its anticholinergic effects on the GI tract that would delay gastric emptying[58]. However, there is less conclusive evidence showing that GL has clear effects on CBZ poisoning[59,60]. As noted in a position statement related to GL use, GL should not be considered unless a potentially life-threatening amount of a poison is ingested by the patient, and this approach should be initiated within 60 min of ingestion[61]. Nevertheless, the clinical benefit has not been confirmed in controlled studies. Moreover, GL is not appropriate for all patients, and not all patients can benefit from GL. GL is contraindicated in patients who have impaired consciousness, recent surgery, no protection of the airway, risk of GI bleeding and perforation, and potentially increased risk and severity of aspiration[57]. The major complications of GL include perforation of the esophagus and stomach, pulmonary aspiration, and aspiration pneumonia[62].

MDAC

AC therapy is still the most frequently employed method of GI decontamination for acute drug overdoses in developed countries. With a highly developed internal pore structure, the tremendous surface area of AC permits the adsorption of drugs and toxins in the GI tract within minutes of contact, which reduces their systemic absorption and subsequent toxicity and enhances their elimination[63]. AC therapy involves SDAC and MDAC, which indicates scheduled administration of more than two small doses of AC.

MDAC should only be considered if a patient has ingested a life-threatening amount of CBZ. MDAC therapy is effective in poisoning due to three distinct mechanisms: (1) Reducing ongoing absorption of extended or delayed-release formulations remaining in the gut[49]; (2) Interfering with enterohepatic and enterogastric circulation of drugs[64-66]; and (3) Promoting the diffusion of drugs from circulation into the gut lumen and trapping them there to be discharged later in the excrement (this process is sometimes called "GI dialysis")[67].

The "routine" use of MDAC has not been shown to reduce morbidity and mortality in poisoned patients in controlled clinical trials. However, evidence from animal and volunteer studies, as well as poisoning cases, indicates that MDAC therapy significantly enhances total body clearance and shortens the half-life of CBZ[33,68-71]. Mittag *et al*[19] recently reported a case of CBZ overdose in which the patient was treated with AC (1 g/kg body weight); his CBZ concentration dropped from the initial value of 41.5 mg/L to approximately 12 mg/L after 24 h. A randomized crossover study in 5 fasted volunteers performed by Neuvonen and Elonen[65] showed that the elimination of CBZ could be significantly enhanced by MDAC. In a study by Boldy *et al*[70] involving 15 patients with CBZ poisoning, researchers gave patients MDAC therapy and found that the mean half-life decreased to 8.6 ± 2.4 h and the mean total body clearance increased to 113 ± 44 mL/min. By comparison, the mean elimination half-life in another two groups of patients managed with supportive treatments only was approximately 19 h[8,72]; similar conclusions have been reached in other studies[73,74].

MDAC enhances the clearance of CBZ in the body and has been approved by the latest joint statement issued by the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists [64]. The statement recommends that MDAC be considered only if a patient has ingested a life-threatening amount of CBZ. In addition, several conditions are considered contradictions including an unprotected airway, the presence of intestinal obstruction, and a GI tract not anatomically intact. Attention should be paid to prevent complications such as constipation, ileus, and aspiration pneumonia in an unprotected airway, although these occurrences are rare[75].

The efficacy of AC is inversely related to the time elapsed after the ingestion of toxic substances[42,76]; thus, administration of charcoal as soon as possible yields the best results. However, the considerably delayed absorption of drugs is often noted in cases of acute poisoning due to inhibition of gastric emptying and gut motility and the limited solubility of drugs, among other reasons[21,22]. Therefore, AC administration is apparently indicated if delayed or prolonged absorption is anticipated, even after a delay of 24-48 h[75].

There is no established optimal dosage regimen for AC; however, available data indicate a dose-response relationship: An AC: Drug ratio of 10:1 or higher is considered optimal for AC adsorption[77-79]. However, the efficacy of AC is influenced by many variables, making it difficult to administer the optimum dose[63]. Consequently, in practice, a fixed dose of 1 g/kg is generally recommended with the maximum amount not exceeding 50-70 g. A flexible dose of 0.25-1.0 g/kg is used for MDAC, and the dosing interval varies based on laboratory (*e.g.*, increasing blood concentrations) or clinical evidence for continuing drug absorption and ranges from 1 h to 4 h. Vomiting is an important factor to consider when substantial doses of AC are administered repeatedly. Continuous nasogastric infusion of AC or frequent administration of AC with smaller doses, at least following a large initial dose (50-100 g), may contribute to reduced vomiting[80,81]. In some cases, the combined use of antiemetics, such as metoclopramide or ondansetron, may have desirable effects.

ECTR

ECTR, also known as blood purification treatment, is a medical technology that removes poison from the blood by moving the blood from the patient into a purification device. ECTRs are classified based on their mechanism:

Hemodialysis (HD) and peritoneal dialysis act by diffusion; hemoperfusion (HP) acts by adsorption; hemofiltration acts by convection; and therapeutic plasma exchange acts by centrifugation[82,83]. Each technique has a potentially different role in eliminating poison from the body. Whatever modality is used, optimizing ECTR characteristics to achieve maximum removal of poison is crucial; for example, higher flow rates of blood and dialysate, filters with larger surface area, and longer duration of ECTR maximize poison removal[84].

According to the EXTRIP workgroup on the use of ECTR in CBZ poisoning, ECTRs are recommended for patients with significant or potentially significant clinical poisoning because they are preferable interventions for rapidly and substantially removing CBZ[5]. Even when considering its weaknesses, such as high risks, high costs, and relative uncertainty, ECTR is generally considered by the workgroup to be worth implementing in patients with severe CBZ poisoning (as manifested by signs such as multiple refractory seizures, hemodynamic instability requiring vasopressors, or life-threatening dysrhythmias). ECTR can prevent the worsening of CBZ poisoning symptoms such as severe hypotension, as well as comatose complications associated with chronic shortness of breath such as ventilator-associated pneumonia and pulmonary emboli[5]. In addition, ECTR is expected by most participants in the workgroup to be a potentially cost-saving technique by minimizing the mechanical ventilation period and residence time in the intensive care unit (ICU), ultimately reducing ICU-related costs[5]. Whether and when to initiate ECTR should be primarily based on clinical symptoms and signs, rather than serum CBZ concentrations, although more severe toxicity apparently occurs when CBZ concentrations are > 40 mg/L[21,85]. The optimal duration of extracorporeal removal should be adjusted to the patient's clinical condition and CBZ levels. Furthermore, the continuous and regular monitoring of CBZ serum concentrations after ECTR is essential, as concentrations may rebound[86]. If concentrations rebound to threatening levels or if there is a recurrence of toxic symptoms, another session of ECTR may be required. ECTR is recommended for patients with significant or potentially significant clinical poisoning. Intermittent HD is the preferred modality for ECTR in CBZ poisoning. Intermittent HP and continuous renal replacement modalities are alternatives if intermittent HD is not available.

HP: HP refers to anticoagulated blood that circulates through a cartridge containing adsorbent particles (AC particles or resin beads) onto which the poison can be adsorbed to achieve the goal of blood purification[87,88]. This modality is suitable for removing poisons with medium or large molecular weight, high lipid solubility, and high protein binding. CBZ is a highly lipid-soluble drug that can be rapidly distributed in tissues, and its plasma protein binding is as high as 70%-80%. Therefore, HP is historically identified as the preferred modality for extracorporeal removal in cases of severe CBZ poisoning[89-92], although the EXTRIP workgroup published a contrary opinion. Despite limitations such as early saturation of the cartridges, the successful removal of CBZ through either resin or charcoal HP has been reported with varying clearance efficiencies ranging from 25% to 55%[93-97]. In a recent study conducted by Yang *et al*[98], the authors concluded that the early initiation of HP during treatment of CBZ poisoning would significantly lower the serum concentration and minimize the CBZ detection time, leading to symptom relief and shortening of the overall treatment period. However, this procedure is often difficult to perform and carries risks such as thrombocytopenia, leukopenia, coagulopathy, and hypocalcemia, which are thought to be associated with cell adsorption and continuous replenishment of the AC[99,100]. Therefore, the frequent monitoring of platelet counts or application of new biocompatible polymer membranes is indispensable for decreasing these complications[101].

HD: HD takes advantage of the principle of diffusion, allowing poison to pass through a semipermeable membrane from a higher- to lower-level side to remove the poison in the blood. This modality is suitable for poisons with high water solubility, low molecular weight (< 500 D), medium molecular weight, and low protein binding. Although intermittent HP is historically preferred for the removal of CBZ, HD should be considered based on its theoretical superiority in clearing protein-bound poisons such as CBZ, and the EXTRIP workgroup recommends intermittent HD over HP. Indeed, several factors prove that HD is superior to HP. First, its clearance efficiency is superior. Although a previous study showed that HP has higher clearance than HD, the comparison was based on older, less efficient cuprophane dialyzers [5]. Recent data have shown that high-efficiency HD is almost as effective as charcoal HP and results in rapid clinical improvement[13,102-104] when equipped with a highly permeable high-flux membrane with increased dialysate flow, which produces comparable efficacy by allowing the removal of larger molecules and highly protein-bound poisons[105-109]. In addition, there is a risk of hemolysis. Blood flow circulating in cartridges during HP remains limited to 300-350 mL/min; however, the use of brand new catheters during HD enables blood flow up to 400 mL/min[110]. Furthermore, there are high amounts of free CBZ molecules and its metabolites in blood at increased concentrations, which are good candidates for removal by HD[111,112]. Second, the manipulability of HD is superior; HD is more available than HP, and HD is the preferred technique for dialysis for patients with acute kidney injury and end-stage kidney disease worldwide. Early initiation of ECTR is critical, considering that clinical improvements are likely associated with how quickly poisons can be cleared from the body. In addition, physicians and nurses are more familiar and experienced with HD; thus, this technique is more likely to be implemented with fewer delays and uncertainties. Third, outcomes of HD are superior; complications are less likely to occur with HD than with HP[113]. Finally, HD has a favorable cost compared with HP. A recent investigation of availability, time to initiation, and cost of ECTR in acute settings worldwide confirmed the lower cost of HD compared with other ECTRs (median cost ratio of HP:HD = 1.7)[114]. The high spending associated with HP is largely due to multiple replacements of expensive charcoal cartridges because of its easy saturation, which would decrease poison clearance[12,91]. Moreover, monitoring and treating complications of HP contribute to its high expenses.

Continuous renal replacement treatment: Continuous renal replacement treatment (CRRT), also known as continuous blood purification, is a treatment involving the continuous, slow removal of water and solutes. CRRT includes continuous venovenous HD, continuous venovenous hemodiafiltration (CVVHDF), and continuous venovenous hemofiltration[115]. These continuous therapies are usually performed in the ICU to facilitate management of hemodynamically unstable patients who cannot withstand high-efficiency intermittent treatments. Therefore, lower dialysate rates during CRRT (up

to 10 L/h) than the dialysate flow rates used in intermittent HD (500–800 mL/min) are routinely offered, leading to markedly lower clearance[5]. However, CRRTs play a better role in mitigating rebound effects than intermittent techniques, regardless of the drug clearance rate. Numerous studies are available documenting the use of CRRTs in patients with CBZ intoxication; however, techniques and outcomes vary substantially. Thus, the benefits of these techniques to eliminate CBZ from the body are unable to be determined[89,116-119]. Consequently, continuous techniques are regarded as low-priority modalities by the EXTRIP workgroup and are only advocated when intermittent treatments are unavailable (because of technical or personnel reasons in critical care settings). Nevertheless, some authors approve of the joint use of intermittent procedures and CRRTs in patients with poisoning to avoid "rebound phenomenon".

Recently, the addition of albumin to the dialysate appeared to improve CBZ clearance compared with conventional CRRT in some studies[120-124]. In a study conducted by Choi *et al*[122], the applied CVVHDF showed a 24% increase in CBZ clearance when using dialysate with the addition of 20% albumin. Another *in vitro* study using modeled continuous HD performed in 2009 also confirmed that CBZ clearance was significantly enhanced with 2.5% or 5% albumin-supplemented dialysate compared with control (albumin-free) dialysate[123]. This technique could be explained by basic principles of thermodynamic protein-binding affinity and solute movement along a concentration gradient. The albumin added to the dialysate works as a "sink" to bind CBZ that moves across the dialyzer membrane along the concentration gradient formed between the blood side and dialysate side[124]. However, extremely high costs have limited their widespread use. In addition, whether these procedures have superiority to either HP or HD remains unclear and further investigation is needed.

LRT

LRT is a relatively new method to improve the clinical manifestations of toxicity from overdose of certain drugs through administration of intravenous lipid emulsions (ILEs). ILE was conventionally used for parenteral nutrition and first applied in 1998 by Weinberg and colleagues[125] as a treatment option in toxicology. The first human case of ILE clinical use was reported by Rosenblatt *et al*[126] in 2006 to treat local anesthetic (bupivacaine) systemic toxicity. Since then, ILEs have been widely used in clinical toxicology as a life-saving treatment for local anesthetic-induced cardiotoxicity[127]. With further research, the field has expanded progressively with successful clinical translation and expansion of use to treat other types of non-local anesthetic lipophilic drug overdoses[128-132].

The ILE mechanisms of action are not entirely clear but can be partially explained by dynamic scavenging/partitioning and direct cardiovascular effects[133,134]. In 1998, Weinberg and colleagues originally proposed a mechanistic hypothesis, namely, that ILE provides a novel compartment into which lipophilic drugs circulating in the blood are able to partition, preventing them from affecting other organs. This theory was widely accepted and referred to as "the lipid sink". However, with improved understanding of this treatment, a "lipid shuttle" or a capture/release mechanism has been suggested in which ILEs play a role in accelerating the redistribution of drugs and moving drugs around, as opposed to acting like a "lipid sink" that catches and segregates drugs[135]. In addition, ILEs exert direct effects on myocardial tissue that improve cardiac output; however, the relevant potential mechanisms are not fully understood[136, 137]. Based on these mechanisms of action, ILEs have been used to manage toxicity from non-local anesthetic lipophilic drugs.

CBZ is a highly lipophilic molecule and can induce cardiotoxicity in cases of significant overdose. ILEs have been administered to treat CBZ intoxication in several cases with varying results[116,138-141]. ILE treatment was used in two case reports for CBZ-induced cardiotoxicity and showed beneficial effects[138,139]. In a retrospective study investigating the clinical effects of lipid emulsion for the treatment of childhood CBZ poisoning, researchers enrolled 48 patients and divided them into Group A (lipid emulsion + HP) and Group B (HP); a statistically significant difference was not observed in the blood concentration of CBZ between groups ($P > 0.05$). After 24, 48, and 72 h of treatment, the CBZ blood concentration in Group A was significantly lower than that in Group B ($P < 0.05$), and the researchers concluded that the lipid emulsion could be used for the treatment of CBZ poisoning in children to reduce the blood CBZ concentration as quickly as possible[142]. Although the sole effect of ILE in CBZ clearance has not been proven, ILE is still considered to be a potentially beneficial alternative to ECTR methods in CBZ intoxication. Whether and when to initiate LRT is discretionary and depends on the clinical judgment of the treating physician. Blood clotting and fat deposition commonly occur in extracorporeal circuits when combined with LRT[140,141], and thus should be monitored during therapy.

DISCUSSION

We conducted a retrospective review of selected literature. The case reports contained detailed data describing patient status and treatments, and an aggregate description was made (Table 1). After discussion and analyses of CBZ poisoning cases, we established recommendations for the treatment of CBZ poisoning (Table 2); 67 patients were included and no randomized controlled trials were identified. The median CBZ peak concentration was 39.0 mg/L and the median age was 42.3 years. Notably, all patients had varying degrees of consciousness impairment, which were due to individual differences. In addition, some patients experienced respiratory depression, dysrhythmias, hypotension, seizures, or a combination of these symptoms. Among the patients, 32 showed varying degrees of respiratory depression. Overall, 4 cases were described as deaths caused by CBZ poisoning rather than the effect of the treatment[43,44,105]. GL is a simple and convenient treatment, but only 6 patients received GL because the treatment is prohibited in patients with impaired consciousness, recent surgery, no airway protection, risk of GI bleeding and perforation, or potential for increased risk

Table 1 Clinical outcomes of the 67 patients described in the case reports

Patient demographics	Values
Median age (yr)	25 (1.5-85)
Male sex	49.3
Poisoning exposure	
Mean peak carbamazepine concentration in mg/L	39.0 (17.7-93.8)
Clinical symptoms and signs	
Respiratory depression	47.8
Decreased consciousness	100
Seizure	20.9
Hypotension	14.9
Dysrhythmias	19.4
Treatment measure[1]	
Supportive care	9.0
Gastric lavage	29.9
Multiple-dose activated charcoal	58.2
Hemoperfusion	22.4
Hemodialysis	22.4
Continuous renal replacement treatment	12.0
Plasma exchange and plasmapheresis	4.5
Lipid resuscitation therapy	4.5
Outcome	
Recovery	82.0
Sequelae	12.0
Fatalities	6.0

[1]Some patients received more than one treatment.
Data are presented as *n* (range) or %. The source of cases is listed in Supplement Material.

and severity of aspiration[16,19,21,23,26,28]. In these situations, considering the patient's economic conditions and affordability, MDAC was chosen instead of GL. For decades, MDAC has been used as a universal antidote for the majority of poisons because of its ability to prevent absorption of the most toxic agents from the GI tract and enhance the elimination of some agents already absorbed[143,144]. The optimum dose of MDAC is difficult to precisely determine for an individual patient. Optimum dosage depends on many variables such as the volume and pH of gastric and intestinal fluid, and the presence of other agents or food absorbed by AC[145-148]. Notably, repeated administration is still effective against substances that stay longer in the stomach, which is another advantage of MDAC. The recommended dose for adults is typically 50 g; however, the amount administered to children is determined based on body weight (0.5-1 g/kg). Reported complications and adverse effects of MDAC include diarrhea, constipation, vomiting, pulmonary aspiration, and intestinal obstruction. Consequently, MDAC should be used with caution in the following situations: unprotected airway; presence of intestinal obstruction; or GI tract not anatomically intact. Therefore, intestinal motility in patients receiving MDAC should be continuously monitored as necessary to maintain electrolyte and water balance.

HP was the most common treatment for the patients in our review, accounting for 58.2% of cases. HP was considered the most timely and effective treatment for patients with excessive CBZ toxicity and life-threatening symptoms because it can remove mid-to-large-sized toxin molecules bound to proteins. However, the earlier enthusiasm for HP has decreased and HD is currently the treatment of choice for poisoned patients. HP presents some challenges compared with HD. For example, HP is associated with more complications than HD (namely, hypocalcemia, leucopenia, thrombocytopenia[147,148]), and the rate of complications is greater during HP than HD. Furthermore, HP is more expensive and results in the early saturation of columns. Notably, the same percentage of patients received HD and CRRT therapy (22.4%). HD and CRRT are commonly used to provide renal support to critically ill patients with acute kidney injury, particularly those who are hemodynamically unstable. Although initially developed as an arteriovenous therapy, most CRRT is now performed using pump-driven venovenous extracorporeal circuits. However, initiation of CRRT requires vascular access, which is generally established through placement of a large-bore double lumen catheter in an internal jugular, femoral, or

Table 2 Executive summary of recommendations for the treatment of carbamazepine poisoning

General statement
The primary treatment for CBZ poisoning is GL
A mainstay of treatment is multiple-dose activated charcoal
ECTR is suggested in cases of severe CBZ poisoning
Intermittent hemodialysis is the preferred ECTR for CBZ poisoning
Lipid resuscitation therapy is an effective adjunctive treatment to ECTR
Supportive care
Severe central nervous system depression requires endotracheal intubation
To avoid masking subsequent seizures, short-acting neuromuscular blockers are recommended
Isotonic crystalloid to correct hypotension should be considered first; when isotonic crystals do not work, direct-acting vasopressors can be applied
QRS prolongation is treated with sodium bicarbonate
Management precautions
GL is contraindicated when patients have impaired consciousness, recent surgery, no protection of airway, risk of gastrointestinal bleeding and perforation, and the potential for increased risk and severity of aspiration
Multiple-dose activated charcoal should be used with caution in cases of an unprotected airway, presence of intestinal obstruction, or gastrointestinal tract not anatomically intact

CBZ: Carbamazepine; ECTR: Extracorporeal treatment; GL: Gastric lavage.

subclavian vein. Furthermore, hypotension during CRRT is common, occurring in some series in more than one-third of patients, but is most often unrelated to the CRRT procedure. Increased hemodynamic instability due to ultrafiltration may be the most likely treatment-related factor contributing to hypotension[149]. Therefore, we conclude that in the absence of accurate, scientific data indicating effectiveness and risk, a sound recommendation for the use of CRRT cannot be made. Again, the treating physician must weigh the theoretic benefit against the potential for complications in each clinical scenario. HD is indicated for the therapeutic management of acute poisoning or drug overdose and is the most commonly favored extracorporeal technique in poisoning situations due to its availability, cost, and safety profile. With the development of science and technology, the advent of high-efficiency, high-flux dialyzers has rendered other techniques, such as HP, almost obsolete. Furthermore, HD enables the correction of acid-base and electrolyte abnormalities.

Among patients, plasma exchange and plasmapheresis as well as lipid emulsion were the least frequent (both 4.5%). Plasma exchange and plasmapheresis refer to the extracorporeal technique preformed in an apheresis device where the patient's plasma is separated from whole blood and removed, and the cellular blood components are returned to the patient together with a replacement fluid[150]. Therapeutic procedures commonly include therapeutic plasma exchange and red blood cell exchange with or without depletion, in addition to more specialized procedures, such as low-density lipoprotein (LDL) apheresis and extracorporeal photopheresis, which was widely used in China to treat patients with coronavirus disease 2019[151]. However, because performing extracorporeal photopheresis is complex and requires precision, the method is rarely used in drug intoxication cases. The mechanism of action in LDL apheresis creates an expanded, intravascular lipid phase in which equilibria are established that drive the offending drug from target tissues into the newly formed "lipid sink". Based on this theory, LDL has been considered a candidate for generic reversal of toxicity caused by overdose of any lipophilic drug. However, the use of LDL apheresis requires caution, especially in patients with a history of hypersensitivity to lipid emulsion or ingredients (*e.g.*, eggs, soy), severe sepsis, severe liver disease, acute pancreatitis, and acute myocardial infarction. Therefore, we suggest that LDL apheresis be considered under circumstances of refractory hemodynamic instability.

CONCLUSION

Herein, we presented recommendations for therapies in CBZ poisoning. Risk assessment of selected case reports showed that in most poisoned patients, general supportive measures usually suffice, including airway management and protection, ventilatory support, fluid resuscitation, correction of electrolyte and acid-base disorders, and management of poison-related hypo/hyperthermia. Primary GI decontamination with AC and routine GL are widely used. Aggressive ECTR is required for rapid and substantial removal of CBZ and its metabolites when clinical symptoms and signs are serious or deteriorated. Choice of ECTR modality should be based on clearance efficiency, availability, cost, and complications. Among the various ECTRs available, HD provides the best expected removal for CBZ poisoning with the lowest incidence of complications and should therefore be the preferred modality in most cases.

FOOTNOTES

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MINIREVIEWS

Research status of internet-delivered cognitive behavioral therapy in cancer patients

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Abstract

The latest global cancer burden data released by the International Agency for Research on Cancer of the World Health Organization in 2020 shows that there were 19.29 million new cancer cases worldwide, with 4.57 million in China, ranking first. The number of cancer survivors is increasing, with a 5-year survival rate exceeding 85%, but there are emotional disorders. Cognitive behavioral therapy (CBT) can improve negative emotions and has significant effects on patients. However, there is a limited number of physicians and high costs, so internet interventions have become a solution. The feasibility of web-based interventions for breast cancer patients has been proven. Research on internet-delivered CBT is also increasing. The purpose of this study was to review the concept of web-based CBT and its application status in cancer survivors, in order to provide relevant intervention for scholars and provide reference and supplement for patients to provide psychological therapy.

Key Words: Cancer survivors; Network; Cognitive behavioral therapy; Negative emotions

Core Tip: The number of cancer survivors is increasing, but emotional disorders persist. Cognitive behavioral therapy (CBT) has shown significant effects in improving negative emotions. Due to limited physicians and high costs, internet interventions have become a solution. Web-based interventions for breast cancer patients have proven feasible, and research on internet-delivered CBT is growing. It is helpful to reviewing web-based CBT and its application in cancer survivors and provide intervention insights for scholars and psychological therapy references for patients.

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INTRODUCTION

According to the latest global cancer burden data released by the International Agency for Research on Cancer[1] of the World Health Organization, there were 19.29 million new cancer cases worldwide in 2020, and 4.57 million in China, which ranks first in the world. Thanks to improvements in diagnosis and treatment, the number of cancer survivors is increasing, with 5-year survival rates > 85%. Cancer survivors have varying degrees of mood disorders, including negative emotions, cancer-related fatigue, and sleep disturbances. It has been reported that mood disorders in cancer survivors are 2-4 times more prevalent than in the general population, leading to a lower quality of life, poorer daily functioning, and poor prognosis[2,3]. Meta-analyses show that cognitive behavioral therapy (CBT) improves negative mood, with effect sizes of 0.97 and 0.95 for patients with mood disorders, and 0.39 and 0.44 for cancer patients and survivors. However, due to the limited number of trained therapists, high cost, and limited time and space for cancer patients and survivors, providing CBT to patients in need remains a challenge[4]. Interventions delivered *via* the internet have become an increasingly popular way to overcome these challenges, and a review of e-health intervention systems for breast cancer patients and survivors demonstrated the universal feasibility and acceptability of interventions delivered *via* the internet[5]. There are also increasing studies on the intervention of patients with internet-delivered CBT (ICBT)[6-8].

OVERVIEW OF CBT

The origins of CBT can be traced back to Skinner and Joseph[9], who pioneered the CBT movement in the 1950s. CBT refers to changing adverse emotional reactions by correcting irrational cognitive concepts and/or behaviors, so as to resolve a series of physiological and psychological problems in patients[10]. In other words, changing behaviors will lead to emotional and cognitive changes. ICBT provides health education information to patients through the internet[11]. In ICBT, patients can obtain the same health information as CBT (such as psychological education on cognitive behavioral patterns, cognitive reorganization, behavioral skills, and relapse prevention)[12-14]. The material content of ICBT usually includes text, image, video and audio, *etc*., and generally the intervention duration varies from 5 to 15 wk[15]. CBT is a problem-centered and action-oriented approach that aims to eliminate negative emotions and behaviors by changing thoughts and behaviors to change negative cognition[9]. It focuses more on the current situation than on past experiences, mental problems, and connections between wrong ways of thinking and ways of acting, which helps patients to better identify their own negative thinking, use cognitive technology to combat negative thinking, correct wrong cognition to improve anxiety, depression and other negative emotions, and relieve pain, sleep disorders, and other physical and mental symptoms. This study conducted a literature search using the keywords "internet-delivered cognitive-behavioral therapy" or "web-based cognitive-behavioral therapy" and "tumor" or "cancer" on PubMed, China National Knowledge Infrastructure, and Wanfang Database to retrieve relevant Chinese and English articles. After screening, a total of 49 articles were obtained for reviewing the concept of ICBT and its application in cancer survivors.

APPLICATION AND EFFECT OF CBT IN CANCER SURVIVORS

Reducing negative emotions

Compared with healthy people, cancer patients are more likely to experience negative emotions such as anxiety and depression[16]. A large Canadian study on mental disorders in 10153 cancer patients[17] showed that 19% had clinical anxiety symptoms, 22.6% had subclinical anxiety symptoms, 12.9% reported clinical depression symptoms, and 16.5% reported subclinical depression symptoms. Therefore, it is important to find treatment that can improve the psychological problems of cancer patients to improve their prognosis. Palay *et al*[17] found that breast and prostate are common cancer types with high survival rate, and such cancer survivors have some psychological distress, so they developed ICBT to improve the anxiety and depression symptoms of cancer patients in their daily life. The study began with screening of cancer patients at cancer hospitals and controlled follow-up of patients after initial treatment for symptoms of anxiety and depression in their daily lives. A total of 206 cancer patients were recruited for the study. These participants were randomly assigned to either the intervention group or the waiting control group for 10 wk each, with follow-up at week 5 (T2/mid-intervention), week 10 (T3/post-treatment), and week 34 (T4/6 mo post-treatment). The ICBT intervention program for improving anxiety and depression symptoms in cancer patients was developed by clinical psychologists who modified the original face-to-face CBT manual[19,20]. It lasted for 1 wk and consisted of eight modules, each consisting of written materials and audio exercises, writing tasks, examples of cancer patients, and expert videos. Participants completed a weekly training diary and mailed it to a therapist, who gave corresponding asynchronous written feedback[21]. The basic points of this treatment plan are as follows: (1) Nine therapists: Eight CBT-trained masters in psychology and

one experienced psychologist; (2) Supervision: Based on written feedback from therapists to participants, a manual reminder guide was developed, undertaken by therapist assistants, to urge participants to complete online questionnaires at stages T2, T3 and T4. If participants do not complete the questionnaire within 1 wk, they will receive three reminder emails, and if they do not respond, a research assistant will call to ask the reason; (3) Treatment compliance: To improve compliance of participants, researchers will give gifts or bonuses to participants at the middle and end of treatment as incentives; and (4) Internet platform: This is a website compatible with smart phones, and patients carry out daily exercises through their personal accounts. The waiting control group was given a cancer hospital health manual and followed up with a questionnaire at four time points. The study used the State-trait Anxiety Scale, the Patient Health Depression Questionnaire and the World Health Organization Quality of Life Index questionnaire[22-24] (Figure 1).

This study found that 5 wk after intervention, anxiety and depression in the ICBT group were significantly lower than those in the waiting control group[25], indicating that anxiety and depression were improved immediately after intervention. Model fitting analysis showed that depression scores were in line with a log-linear curve, indicating that the improvement in the ICBT group occurred at the beginning of the study and continued to improve over a period of time. At the 6-mo follow-up assessment, the improvement in anxiety and depression was 2.35 times greater in the ICBT group than in the waiting control group, and was effective in maintaining its effect on patients' negative mood. A meta-analysis showed that mindfulness-based behavioral therapy can be used as a basic treatment for emotional rehabilitation of cancer [26], while interventions provided by the internet may alleviate the suffering of cancer survivors who are unable to access face-to-face psychotherapy[27] (Figure 1).

Improving sleep quality

Sleep deprivation can have significant effects on daily functioning, mood, and self-management in cancer survivors. Sheikhzadeh *et al*[28] developed ICBT for breast cancer patients with insomnia by combining mindfulness meditation and CBT for insomnia. The study used two parallel randomized controlled trials in which 50 patients with cancer insomnia were recruited from 10 hospitals and randomly assigned 1:1 to a mindfulness intervention group or an education-only control group. The mindfulness intervention included a 6-wk online self-directed learning module that covered mindfulness meditation, sleep challenges, and behavioral strategies for improving sleep. The intervention strategy focused on using mindfulness as a sleep self-management technique to increase total sleep time and sleep efficiency. The development of the intervention module was published online. Each module each week contains instructional content on sleep and mindful meditation, using interactive text, video and audio meditation. Each module lasts about 20 min and can be completed at a time of the participant's choosing. There is also a message board for interaction with other participants and researchers[29]. During the day, patients communicate with researchers *via* text or email to obtain support. Reminders to complete daily sleep diaries and weekly modules were sent to participants at intervals by text message or email. During the study, participants completed an online or paper sleep diary each morning, which was modified to include symptoms of sleep disturbances and reports of daily meditation practices. At the end of the second week of the program, weekly feedback reports on adherence to the participants' personally recommended sleep schedules were provided *via* email. The control group was given only health education and no mindfulness or meditation (Figure 1).

The study found that ICBT significantly improved insomnia symptoms. After 6 wk of intervention, 71.2% of patients in the intervention group had sustained significant improvement in insomnia and fatigue symptoms. This study innovatively addressed sleep problems in cancer survivors, using a self-managed study design and methodology that was both available and cost-effective for a large number of cancer survivors, and larger randomized controlled trials can be conducted in the future to guide and refine intervention regimens (Figure 1).

Improving cancer-related fatigue

Fatigue is a symptom commonly experienced by cancer survivors at all stages of disease development. Survivors identified fatigue as an important problem that was not adequately addressed by healthcare providers[30]. Fatigue has a greater negative impact on functioning and health-related quality of life than other symptoms such as pain or depression [31-33]. Mak *et al*[34] selected 100 cancer patients with severe fatigue symptoms from 160 patients diagnosed with cancer according to inclusion and exclusion criteria for an 8-wk randomized controlled trial. The project was developed based on MacDonald and O'Hara's 10 elements of mental health[35], with resources for mental health promotion from the World Health Organization and government reports from the United Kingdom and Australia[36,37]. ICBT courses include didactic reading (such as transmitting Buddhist views on the nature of human suffering), experiential learning (such as guided meditation), and everyday life applications (such as developing an awareness of how attachment to letting go of a person can lead to inner peace). In order to improve the user experience, the project improved on the basis of the preliminary design. Weekly health tracking, built-in multimedia in each class, and dynamic content display made the content more interactive. The page and content color coordination, theme consistent graphics, and easy navigation made the web page more aesthetically attractive. The project incorporated the core concepts of traditional Buddhism, including discernment, compassion, impermanence, interdependence and nonattachment. By incorporating our mindfulness training into a traditional Buddhist foundation, the training program was designed to help participants build their own foundation of practice. Such an intention will lay the foundation for continuous and regular practice and may potentially influence the outcome of practice[38,39]. Participants were also given videos of stretching exercises, body scans, and audio of sitting meditation to guide them through the exercises. During the intervention, participants were given worksheets that included a mood diary, cognitive reconstruction, and a healthy lifestyle program to record their responses. All content was developed by members of the research team, who were clinical psychologists and mindfulness practitioners. The control group received routine nursing (Figure 1).

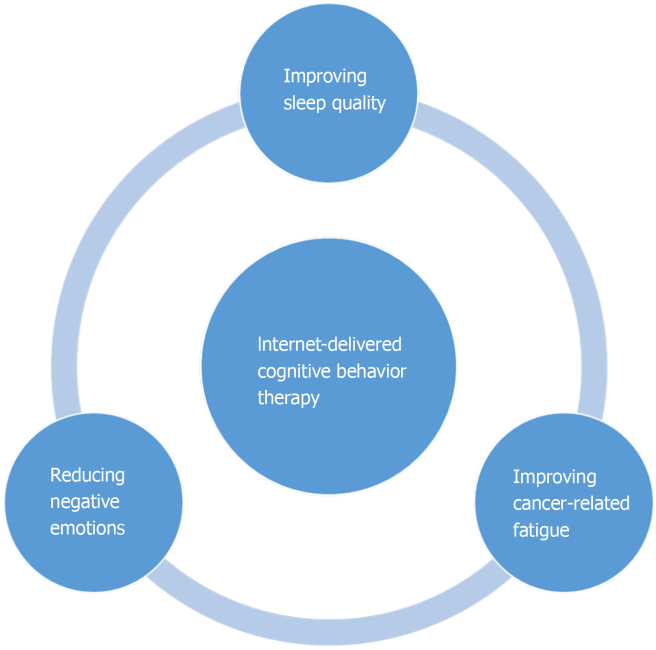

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Figure 1 Application and effect of internet-delivered cognitive behavioral therapy in cancer survivors.

The study used the Cancer Related Fatigue Scale and the European Organization for Cancer Research and Treatment Quality of Life Scale to assess patients' quality of life and fatigue symptoms. The results showed that ICBT could significantly reduce cancer-induced fatigue and improve the quality of life of patients. The web page was designed reasonably, and course of treatment was moderate, with good patient feedback and high treatment compliance. Compared with face-to-face interventions, internet-based interventions are more accessible and affordable, and have the potential to satisfy the need to promote and prevent mental health in community settings and are worth scaling up in the future (Figure 1).

Limitation of ICBT

High dropout rate and poor compliance. Since ICBT courses are carried out in a standardized content and structured format, and therapists are not able to provide timely feedback and adjust the program according to the patient's response, this affects patient compliance[40]. Many complex problems in practice. Implementation of ICBT in five different European countries faced issues such as how to integrate it into the mental health care system, how to recruit patients, how to ensure the quality of the work of therapists, and how to provide long-term sustainable ICBT treatment[41]. Many influencing factors are unclear. At present, there are few studies on factors affecting treatment outcomes. One study explored the influ-encing factors from the content of emails from patients and therapists, and found that affirmation, encouragement, and self-exposure by therapists had a positive impact on treatment outcomes[42].

CONCLUSION

CBT is commonly used as first-line treatment for cancer survivors[43], and the American Medical Association recommends[10] that CBT be administered personally by trained therapists to promote self-management in cancer patients. Face-to-face CBT has been proven to be effective and worthy of promotion, but due to time, space and economic constraints, not all patients can easily access this treatment. With the increasing popularity of the internet, the combination of the internet and continuous care, and the full use of the advantages of the internet, can achieve the goal of promoting health education and prevention. ICBT has the advantages of low cost, easy access, and not being limited by time and space. ICBT can promote cancer patients' self-management, improve negative emotions, improve sleep quality, and relieve cancer-induced fatigue[44-46].

The research of the application of ICBT in cancer patients were summarized in Table 1. In the future, researchers can explore the influence of the duration of ICBT intervention on the intervention effect, so as to select the appropriate intervention time. It is imperative to cultivate high-quality therapists with a background in psychological medicine. In addition, ICBT is a psychological intervention that requires high-quality, multicenter, and large-sample randomized controlled trials. Qualitative interviews and descriptive data collection can be carried out to understand patients' subjective feelings, and improve intervention methods and guide intervention research.

Table 1 Research of the internet-delivered cognitive behavioral therapy application in cancer patients

Ref.	Patients (*n*)	Intervention	Indicators	Conclusion
Nissen *et al* [18]	Cancer survivors (1282)	Therapist-assisted iMBCT	Outcomes of anxiety and depression	iMBCT is a helpful intervention for cancer survivors suffering from symptoms of anxiety
Zachariae *et al*[47]	Breast cancer survivors (255)	ICBT-i or waitlist control	Sleep-related outcomes	ICBT-i appears to be effective in breast cancer survivors, with additional benefit in terms of reduced fatigue
Nissen *et al* [48]	Breast- and prostate cancer survivors (82)	iMBCT	Improvement in anxiety and depression scores from baseline to post-treatment and from baseline to six-months follow-up	iMBCT can be provided for cancer survivors regardless of their age, educational level, and time since diagnosis (up to five years) and therapeutic alliance is not crucial for treatment response
Dirkse *et al* [49]	Cancer survivors with symptoms of anxiety or depression (86)	ICBT program guided by a technician	Anxiety, depression, fear of cancer recurrence, quality of life	ICBT was associated with improved levels of anxiety, depression, fear of cancer recurrence, and quality of life
Murphy *et al*[50]	Breast cancer patients with generalized anxiety disorder (14)	ICBT	Health status, adherence, acceptability	ICBT has significant potential to be a suitable modality supervised by clinican
Murphy *et al*[51]	Cancer survivors (114)	ICBT or TAU	Anxiety and depression symptoms, fear of cancer recurrence, quality of life	Clinician-supervised iCBT has significant benefits for cancer survivors with clinical depression and anxiety disorders
Carbajal-López *et al*[52]	Gastrointestinal stromal tumors (99)	ICBT or internet-delivered cognitive program	General fatigue, reduced motivation, distress and global health status	Both intervention programs showed reductions in the dimensions of fatigue and improvements in distress and dimensions of quality of life

iMBCT: Internet-delivered mindfulness-based cognitive therapy; TAU: Treat-as-usual; ICBT: Internet-delivered cognitive behavioral therapy.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Effects of combined spinal-epidural anesthesia on anxiety, labor analgesia and motor blocks in women during natural delivery

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Abstract

BACKGROUND

The background of this study was analgesia in natural delivery. The combined spinal-epidural anesthesia has obvious analgesic effect on the parturients in natural labor, and combined spinal-epidural anesthesia has been widely used in anesthesia for various diseases.

AIM

To study the effects of combined spinal-epidural anesthesia on anxiety, labor analgesia, and motor blocks in parturients during natural delivery.

METHODS

A total of 120 women who gave birth at Changning District Maternal and Child Health Hospital between December 2021 to December 2022 were included; a random number table approach was employed to divide the women into a control group and a joint group, with each group consisting of 60 women. The control group was given epidural anesthesia, while the joint group was given combined spinal-epidural anesthesia. The visual analog scale (VAS) was used to evaluate the degree of maternal pain. Comparisons were made between the two groups' conditions of childbirth and the duration of labor. Apgar scores were used to evaluate the status of the newborns at birth; Self-rating Anxiety Scale (SAS) and General Self-Efficacy Scale (GSES) scores, umbilical artery blood gas analysis indices and stress indices were compared between the two groups; and the frequencies of motor block and postpartum complications were analyzed.

RESULTS

In comparison to the control group, in the joint group, the VAS scores for the first, second, and third stages of labor were lower ($P < 0.05$). The rates of conversion to cesarean section and postpartum blood loss in the joint group were lower than those in the control group ($P < 0.05$). No significant differences were observed in the Apgar score, the duration of the first stage of labor, or the total duration of

labor between the two groups ($P > 0.05$). The second and third stages of labor in the joint group were shorter than those in the control group ($P < 0.05$). When compared to the control group, the postpartum SAS score of the joint group was lower, while the GSES score was greater ($P < 0.05$). Between the control group and the joint group, the differences observed in pH, arterial carbon dioxide partial pressure, arterial oxygen partial pressure, or arterial hydrogen ion concentration were not significant ($P > 0.05$). Nitric oxide, cortisol, and adrenaline levels were lower in the joint group than in the control group ($P < 0.05$). There were no substantial differences in Bromage grade or rate of complications between the two groups ($P > 0.05$).

CONCLUSION

For parturients during natural delivery, combined spinal-epidural anesthesia can reduce anxiety, provide labor analgesia, shorten labor time, and reduce postoperative stress levels but did not result in a motor block.

Key Words: Combined spinal-epidural anesthesia; Natural delivery; Anxiety level; Labor analgesia; Motor block

Core Tip: The pain of parturients in natural delivery is serious. Spinal anesthesia and epidural analgesia are widely used, but the analgesia effect is not good, and the nerve block effect of lumbar epidural anesthesia is better. The objective of this study was to compare the effects of combined epidural and lumbar anesthesia on labor analgesia and movement block.

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INTRODUCTION

Labor is a complicated physiological and psychological process, and labor pain is a subjective feeling of the human body that lacks objective indicators. Currently, combined spinal-epidural anesthesia is widely used to relieve the pain of parturients during natural childbirth, which has less impact on contraction pain than other analgesic methods[1]. However, various research studies have shown that epidural anesthesia alone has a poor analgesic effect in parturients. Based on this fact, intraspinal anesthesia can be used to effectively enhance the analgesic effect[2]. Combined spinal-epidural anesthesia has a more rapid analgesic effect and better nerve block efficacy than epidural anesthesia[3]. Childbirth is a natural biological process as well as a complex period involving volatile emotions. Related research suggests that the intensity of labor pain is associated with individual pain thresholds as well as many other influencing factors[4]. Poor mood around the time of delivery can directly reduce a woman's pain threshold, making her more sensitive to pain. In addition, severe pain during childbirth increases the fear, tension, and anxiety of parturients, forming a vicious cycle, which keeps them in a state of high stress and has adverse effects on delivery[5,6]. Therefore, reducing negative emotions in patients during childbirth is crucial for smooth deliveries. Based on the above, this study explored the effects of combined spinal-epidural anesthesia on anxiety levels, labor analgesia and motor blocks in women during natural delivery, with the view of selecting a better method of labor anesthesia and promoting smooth deliveries.

MATERIALS AND METHODS

Clinical data

A total of 120 women who gave birth in Changning District Maternal and Child Health Hospital from December 2021 to December 2022 without signs of cesarean section were studied. By employing a random number table, they were separated into control and joint groups, each of which included 60 women. Table 1 demonstrates that no significant differences were present in the general data between the two groups ($P > 0.05$).

The inclusion criteria were as follows: (1) Women aged 23-34 years old; (2) Women with American Society of Anesthesiologists physical status grade I; (3) Primiparas; and (4) Women with a gestational age of 36-40 wk. The exclusion criteria were as follows: (1) Patients with a medical history of hematological diseases; (2) Patients with long-term use of anticoagulants or drugs that affect coagulation function; (3) Patients with contraindications for combined spinal-epidural anesthesia; and (4) Patients with pregnancy-induced hypertension and other obstetric complications.

Methods

The joint group was given combined spinal-epidural anesthesia. When the uterine orifice was opened to 1 cm, puncture was performed in the lumbar L2-3 space. After successful subarachnoid puncture, cerebrospinal fluid flow was

Table 1 Comparison of general data between the two groups

Classification	Joint group (*n* = 60)	Control group (*n* = 60)	*T* value	*P* value
Age (yr)	26.79 ± 3.18	27.03 ± 3.21	0.411	0.682
Gestational age (wk)	39.35 ± 0.24	39.28 ± 0.21	1.700	0.092
Number of pregnancies	1.84 ± 0.17	1.89 ± 0.21	1.433	0.154
Parity	1.59 ± 0.12	1.61 ± 0.15	0.806	0.422
Estimated newborn body mass (kg)	3.58 ± 0.53	3.65 ± 0.49	0.751	0.454

continuous. A subarachnoid injection of 1 μg sufentanil (Yichang Humanwell Pharmaceutical Co., LTD., batch number: SFDA approval number H20054171) and 0.2 mg ropivacaine (Jiangsu Hengri Pharmaceutical Co., LTD., batch number: SFDA approval number H20060137) was given. Epidural catheterization was performed. After successful catheterization, 3 mL of 1.5% lidocaine (Shanghai Pujin Linzhou Pharmaceutical Co., LTD., batch number: SFDA approval number H41022244) was given as the experimental dose. After confirming correct placement in the epidural space, the epidural catheter was fixed with adhesive tape. Sufentanil (0.5 μg/mL) and +0.1% ropivacaine was combined with an epidural infusion pump. The first dose of the infusion pump was set at 10 mL, the patient-controlled analgesia dose was set at 9 mL, and the patient-controlled lockout time was 20 min. The infusion pump was turned on 1 h after anesthesia. Epidural anesthesia was given to the control group with the same specific method as that in the joint group.

The observation targets were as follows: (1) Labor pain: The degree of labor pain in each stage of labor was evaluated by employing the visual analog scale (VAS)[7]. The scores ranged from 0-10, and the severity of the pain increased with the score; (2) Childbirth-related conditions: The two groups' rates of conversion to cesarean section, forceps-assisted delivery, and postpartum blood loss and newborn Apgar scores were compared. The Apgar score was utilized to evaluate the status of newborns[8]. The Apgar scores ranged from 0-10, with a score of 10 representing healthy newborns and a score < 7 indicating asphyxia; (3) Labor duration: Between the two groups, the first, second, and third stages of labor as well as the overall duration of labor were compared; (4) Emotion: The Self-Rating Anxiety Scale (SAS) was employed to evaluate the anxiety levels of patients[9]. The scores ranged from 20-80, and a score of > 50 indicated anxiety. The General Self-Efficacy Scale (GSES) was utilized to evaluate the patients' self-efficacy[10], with scores ranging between 10 and 40 points. Higher scores suggested a stronger sense of self-efficacy; (5) Blood gas analysis indices of the umbilical artery: After delivery, 1 mL of umbilical artery blood was extracted with a heparin anticoagulant syringe. Then, the pH, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2) and arterial hydrogen ion concentration (BE) of the maternal umbilical artery were detected by an ABL77 automatic blood gas analyzer (Radiometer, Denmark); (6) Stress index: Before and 3 d after delivery, 3 mL of maternal venous blood was drawn and subjected to centrifugation, serum cortisol (Cor) and adrenaline (ADR) levels were measured by ELISA, and serum nitric oxide (NO) levels were measured by the NO enzyme method; (7) Degree of motor block: The modified Bromage score was employed to evaluate the degree of motor block[11]. Level 0 indicated that there was no motor block, and the lower limbs could be raised; level 1 indicated the inability to lift the thigh; level 2 indicated difficulty in bending the knee; and level 3 indicated difficulty in bending the ankle; and (8) Complications: In both groups, the frequency of postoperative issues such as hypotension, nausea, and vomiting was measured.

Statistical analysis

SPSS 22.0 software was utilized to process the data. Counting data are reported as percentages, and differences between groups were compared by Fisher's exact test or the χ^2 test. Measurement data are reported as mean ± SD after the normality test, and the differences between groups were compared *via t* tests. Ranked data were analyzed by *Z* tests. $P < 0.05$ indicated a statistically significant difference.

RESULTS

Comparison of labor pain between the two groups: Before anesthesia, no significant difference was observed in the VAS scores of the two groups ($P > 0.05$). In comparison to the control group, in the joint group, the VAS scores for the first, second, and third stages of labor were lower ($P < 0.05$) (Figure 1).

Comparing the childbirth-related conditions between the groups: The rates of conversion to cesarean section and postpartum blood loss were lower in the joint group than in the control group ($P < 0.05$); no significant differences were observed in the two groups' Apgar scores ($P > 0.05$) (Table 2, Figure 2).

Comparison of labor duration between the two groups: The initial stage of labor and the overall duration of labor did not substantially differ between the two groups ($P > 0.05$); the joint group experienced slightly shorter second and third stages of labor in comparison to the control group ($P < 0.05$), as shown in Figure 3.

Comparison of anxiety and depression between the two groups: Prenatal SAS and GSES scores did not differ significantly between the groups ($P > 0.05$). The SAS scores of both groups were lower in the postpartum period than the prenatal period, and the SAS scores of the joint group were lower than those of the control group ($P < 0.05$). The GSES scores were higher in both groups in the postnatal period compared to the corresponding scores in the prenatal period,

Table 2 Comparison of childbirth-related conditions between the two groups

Group	*n*	Rate of conversion to cesarean section	Rate of forceps-assisted delivery
Joint group	60	0.00 (0)	3.33 (2)
Control group	60	8.33 (5)	6.67 (4)
P value		< 0.05	> 0.05

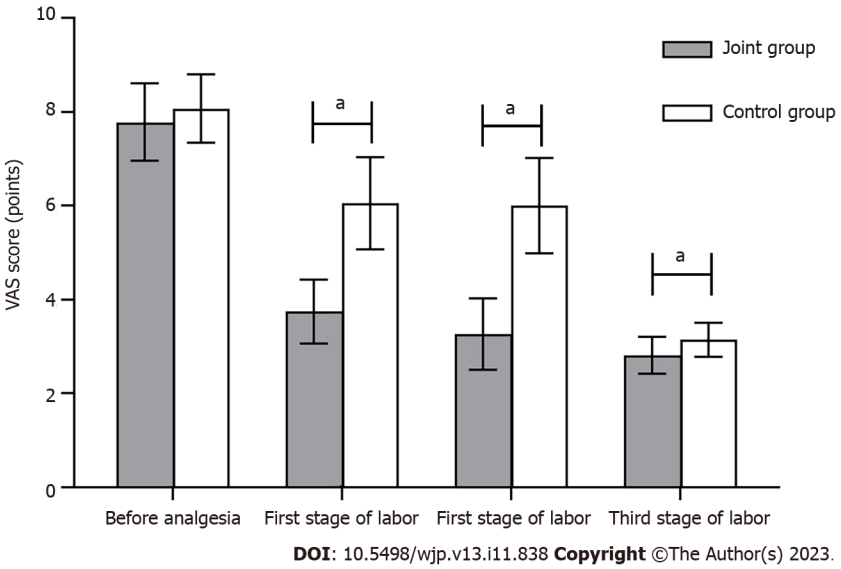

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Figure 1 Comparison of visual analog scale scores between the two groups (scores). [a]*P* < 0.05, comparison with the joint group in the same period. VAS: Visual analog scale.

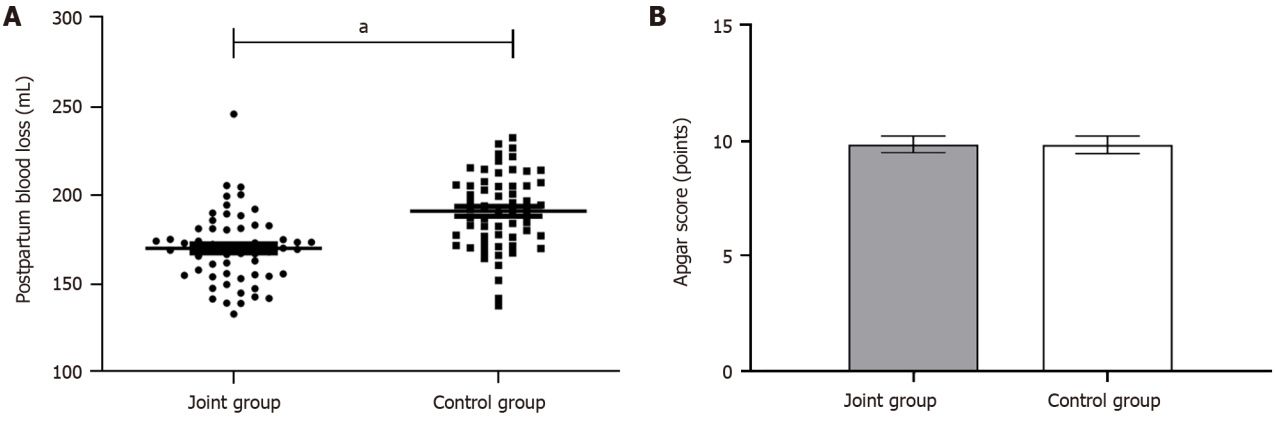

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Figure 2 Comparison of childbirth-related conditions between the two groups. A: Comparison of postpartum blood loss between the two groups; B: Comparison of apgar score between the two groups. [a]*P* < 0.05, comparison with the joint group.

with the joint group having higher scores than the control group ($P < 0.05$) (Figure 4).

Comparison of blood gas analysis indices of the umbilical artery between the two groups: The changes observed in pH, PCO_2, PO_2, and BE between the control and joint groups were not significantly different ($P > 0.05$), as shown in Figure 5.

Comparison of stress indices between the two groups: No significant differences were observed in the prenatal Cor, ADR, and NO levels between the groups ($P > 0.05$). Following delivery, the levels of Cor, ADR, and NO increased in both groups compared to those before delivery. Additionally, the scores in the control group were elevated compared to those in the joint group ($P < 0.05$) (Figure 6).

Comparison of motor block effects between the two groups: The Bromage grade did not substantially differ between the two groups ($P > 0.05$) (Table 3). Comparison of complication rates between the two groups. The complication rates between the two groups did not differ significantly ($P > 0.05$) (Table 4).

Table 3 Comparison of the motor block effect between the two groups

Group	*n*	Grade 0	Grade 1	Grade 2	Grade 3
Joint group	60	52	7	1	0
Control group	60	46	9	4	1
Z value		2.277			
P value		0.131			

Table 4 Comparison of complication rates between the two groups (cases, %)

Group	Joint group	Control group	χ^2	*P* value
n	60	60		
Hypotension	0	1		
Nausea and vomiting	2	1		
Pruritus	0	1		
Deceleration of fetal heart rate	0	1		
Total incidence	3.33 (2)	6.67 (4)	0.702	0.402

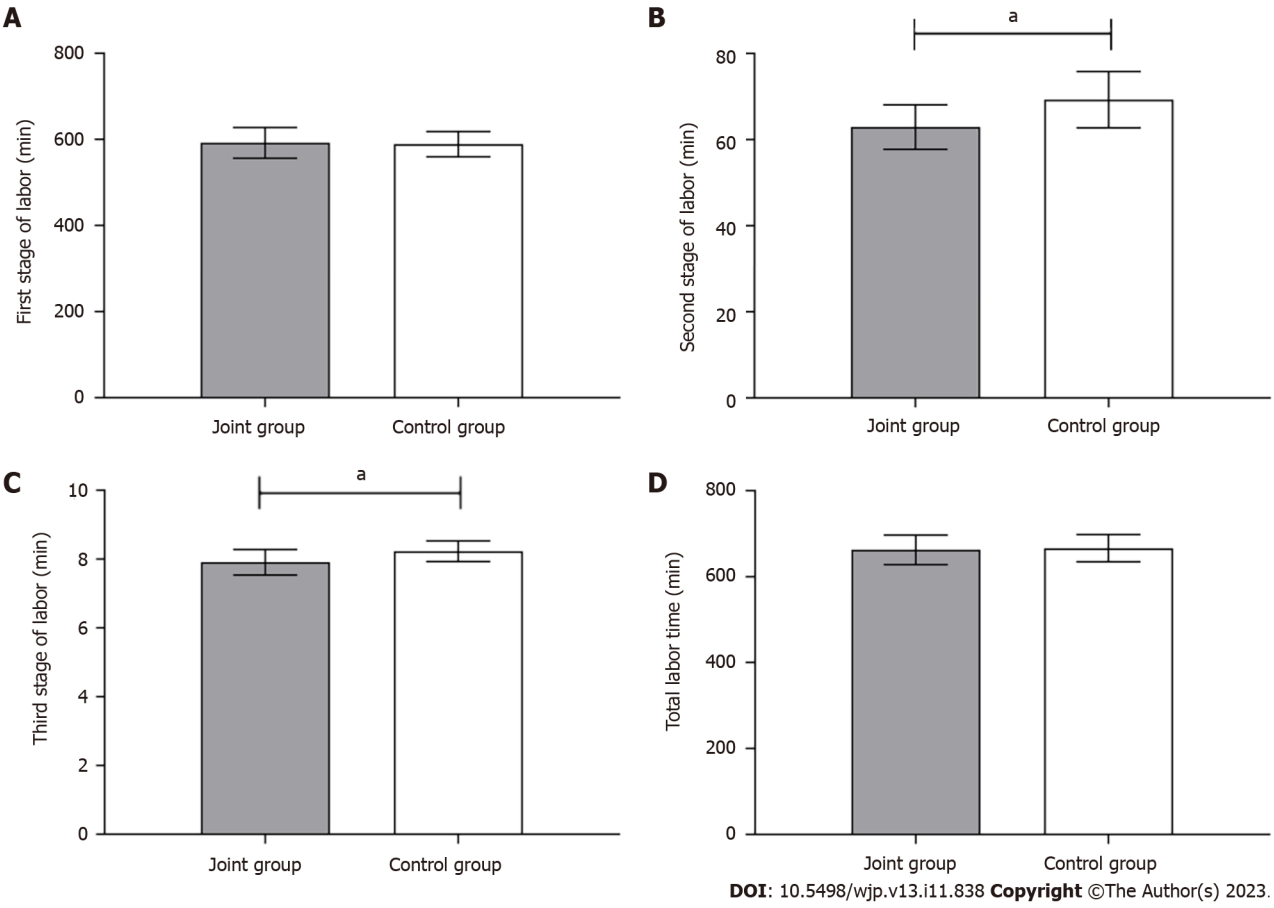

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Figure 3 Comparison of labor duration between the two groups. A: Comparison of the first stage of labor between the two groups; B: Comparison of the second stage of labor between the two groups; C: Comparison of the third stage of labor between the two groups; D: Comparison of the total stage of labor between the two groups. $^aP < 0.05$, comparison with the joint group.

DISCUSSION

Labor pain refers to the pain caused by strong uterine contractions, pelvic floor muscle expansion, and contraction of uterine tissue. Relevant studies have pointed out that intense and sustained pain during natural labor can directly lead to the occurrence of postpartum depression[12]. Hence, it is important to explore a better method of pain relief during labor. Specifically, optimal pain relief during labor can make pain relief easy to control, which is conducive to the smooth progress of labor. Continuous epidural block has been widely used internationally, with exact analgesic effects, lasting effects, little influence on circulation, and no side effects or complications of general anesthesia, such as changes in consciousness, hypoxia, hypercapnia, or aspiration[13]. Previous studies have shown that combined spinal-epidural anesthesia can reduce the pain of women during natural childbirth[14]. Intravertebral analgesia is currently considered by most scholars to be the most effective labor analgesia method. This method can effectively reduce pain during uterine contraction, reduce the stress response during labor, and contribute to the stability of the internal environment of the parturient and the smooth recovery of the body in the postpartum period[15]. The current study revealed that the VAS scores during the first, second, and third stages of labor were lower in the joint group than in the control group, suggesting that combined spinal-epidural anesthesia could alleviate labor pain for women during natural labor, which was consistent with the above research results. However, it should be noted that although combined anesthesia reduces the degree of labor pain, the analgesic drugs used will still have varying degrees of impact on the mother and child, and analgesic drug use during labor can easily hide excessive contractions and can also lead to contraction inhibition. Hence, it is necessary to choose the appropriate delivery method according to the patient's condition. Moreover, the outcomes of the present research demonstrated lower rates of conversion to cesarean section and postpartum blood loss in the joint group than in the control group, suggesting that combined anesthesia can promote the smooth progress of natural delivery. Because pain during labor can be alleviated, a series of physiological changes caused by labor pain can be relieved, and maternal fear and tension can be alleviated, which is conducive to the smooth progress of labor and indirectly reduces the rate of cesarean section[16].

Childbirth is a complex physiological and psychological process that is affected by mental, psychological, and environmental factors. Fear-tension-pain syndrome is common in parturient women. Due to a lack of understanding of the delivery process, an abnormal pregnancy history, existing mental and psychological disorders, and endocrine changes during childbirth, parturient women, especially primiparous parturient women, experience negative emotions such as fear, tension, anxiety, and depression, which are different from those in nonpregnancy[17]. According to literature reports, approximately 5% of the normal population has anxiety, and the incidence of prenatal anxiety can reach 8%-16.5%[18]. Childbirth self-efficacy refers to the belief or confidence that one can apply some techniques to manage and reduce pain during labor. According to some studies, the threshold of childbirth pain for women with poor mental health is reduced, and the psychological advantages generated by the participation of parturients in analgesia can eliminate the tension and anxiety caused by childbirth, increase their self-confidence, reduce the rates of dystocia and childbirth complications, and create favorable conditions for ensuring the safety of the mother and child during childbirth[19]. In the present study, it was found that the SAS score was decreased and the GSES score was increased in the postpartum period in the joint group, implying that the combined spinal-epidural anesthesia improved the sense of self-efficacy and reduced the degree of anxiety. Therefore, medical workers need consider parturients are a whole, determine their mental state in a timely manner, choose safe, rapid, effective, and appropriate analgesic methods, and implement individualized treatment for parturients to achieve ideal labor analgesia. For parturients with low anxiety and depression levels, psychotherapy can be used to comfort them by addressing doubts, relieving tension and loneliness and enhancing maternal confidence in giving birth. In addition, the durations of the second and third stages of labor in the joint group were slightly decreased compared to those in the control group, indicating that combined spinal-epidural anesthesia could reduce the duration of labor in women with natural delivery, which may be related to the reduction of labor pain and anxiety by combined anesthesia.

Umbilical cord blood gas is affected not only by the process of labor but also by placental function, umbilical cord factors, and maternal blood gas status. According to relevant reports, abnormal blood gas indices of cord blood are related to maternal emotions in addition to labor pain[20]. During childbirth, appropriate tension and anxiety can improve a mother's ability to adapt to the environment, which can be accompanied by activation of the sympathetic nervous system. Increased catecholamines acting on α receptors constrict peripheral blood vessels, increase the heart rate, redistribute cardiac output, and ensure the supply of vital organs such as the heart and brain, making up for the shortage of the maternal supply and improving the fetus's tolerance to hypoxia; however, excessive anxiety can affect umbilical cord blood hemodynamics, leading to fetal hypoxia[21,22]. Since the above research results showed that combined anesthesia can help to reduce patients' anxiety, the author believes that this anesthesia method can improve umbilical artery blood gas indices. In the present research, no significant differences were seen in pH, PO_2, PCO_2, and BE between the joint group and the control group, indicating that combined spinal-epidural anesthesia and single epidural anesthesia had little impact on the umbilical artery blood gas indices in parturients who gave birth naturally, which is inconsistent with the relevant research results[23]. This might be due to the study's small sample size; thus, the sample size should be increased for further analysis.

Experiencing high levels of tension, anxiety, and intense pain during labor can trigger a cascade of neuroendocrine reactions within the body. This can lead to elevated levels of catecholamines and adrenal corticosteroids in the bloodstream, resulting in increased oxygen consumption, heightened cardiac burden, uterine vasoconstriction, decreased blood flow, fetal distress, and potential uterine inertia. Pain can cause hyperventilation in parturients, which has adverse effects on their cardiovascular, endocrine, and psychological conditions and can increase the incidence of uterine inertia and uncoordinated uterine contraction. The current study demonstrated that Cor, ADR, and NO levels were comparatively lower in the joint group than in the control group, implying that the combination of lumbar and epidural

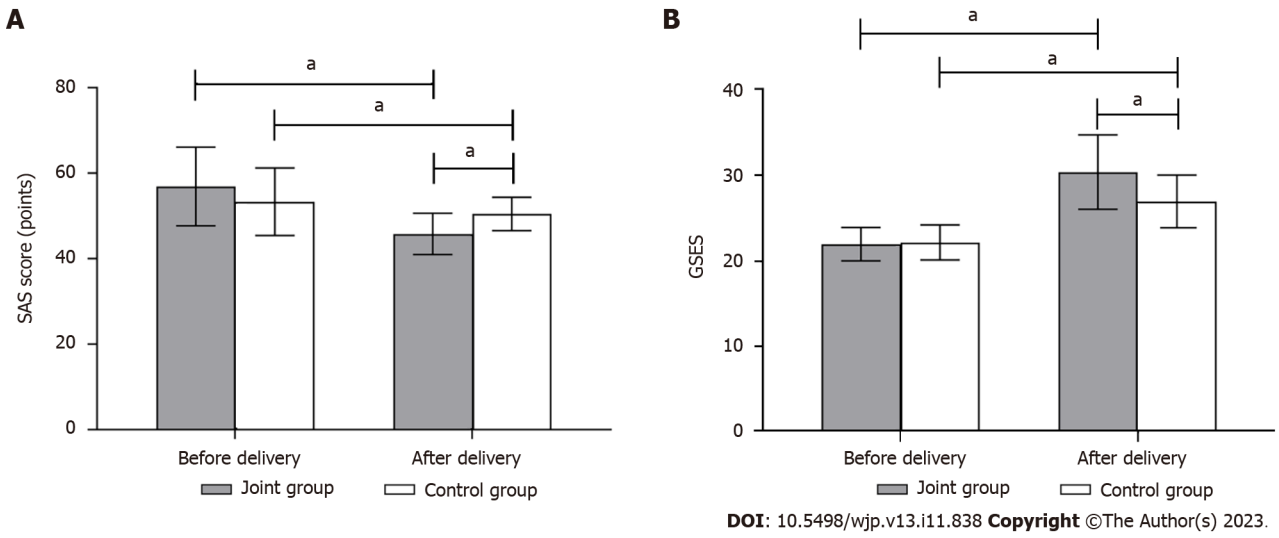

Figure 4 Comparison of anxiety and depression between the two groups. A: Comparison of Self-rating Anxiety Scale score between the two groups; B: Comparison of General Self-Efficacy Scale between the two groups. [a]*P* < 0.05, comparison with the joint group. SAS: Self-rating Anxiety Scale; GSES: General Self-Efficacy Scale.

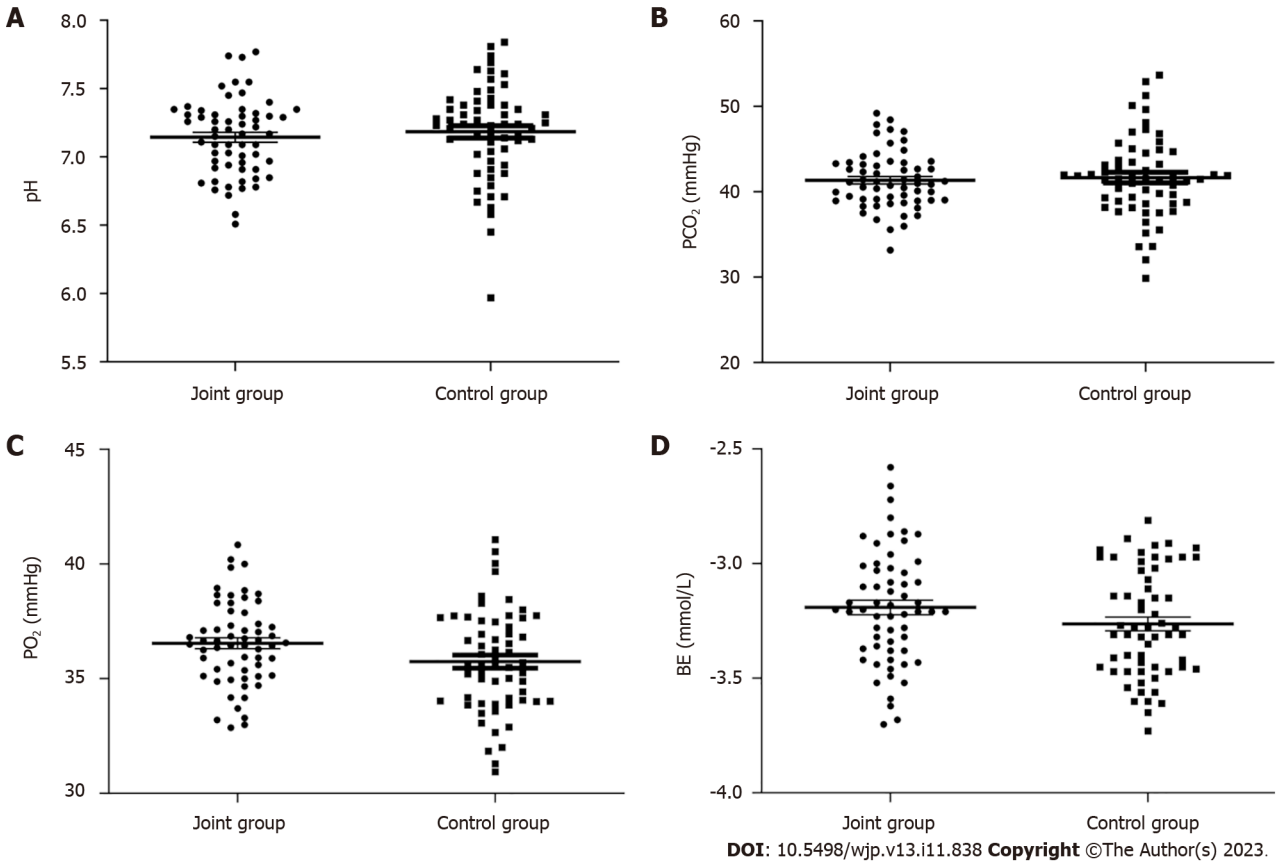

Figure 5 Comparison of blood gas analysis indices of the umbilical artery between the two groups. A: Comparison of pH value between the two groups; B: Comparison of pCO_2 value between the two groups; C: Comparison of pO_2 value between the two groups; D: Comparison of BE value between the two groups.

anesthesia could reduce the postoperative stress level of the body, which was largely associated with the reduction in postoperative pain and improvement in negative emotions of the women in the combined anesthesia group. Related research demonstrates that the degree of motor block can be reduced by giving combined spinal-epidural anesthesia to women during natural childbirth[24]. Nevertheless, no significant differences were found in the Bromage grade or complication rate between the two groups, indicating that combined anesthesia and epidural block alone had little effect on motor block. The reason for this remains unknown, so further analysis should be conducted.

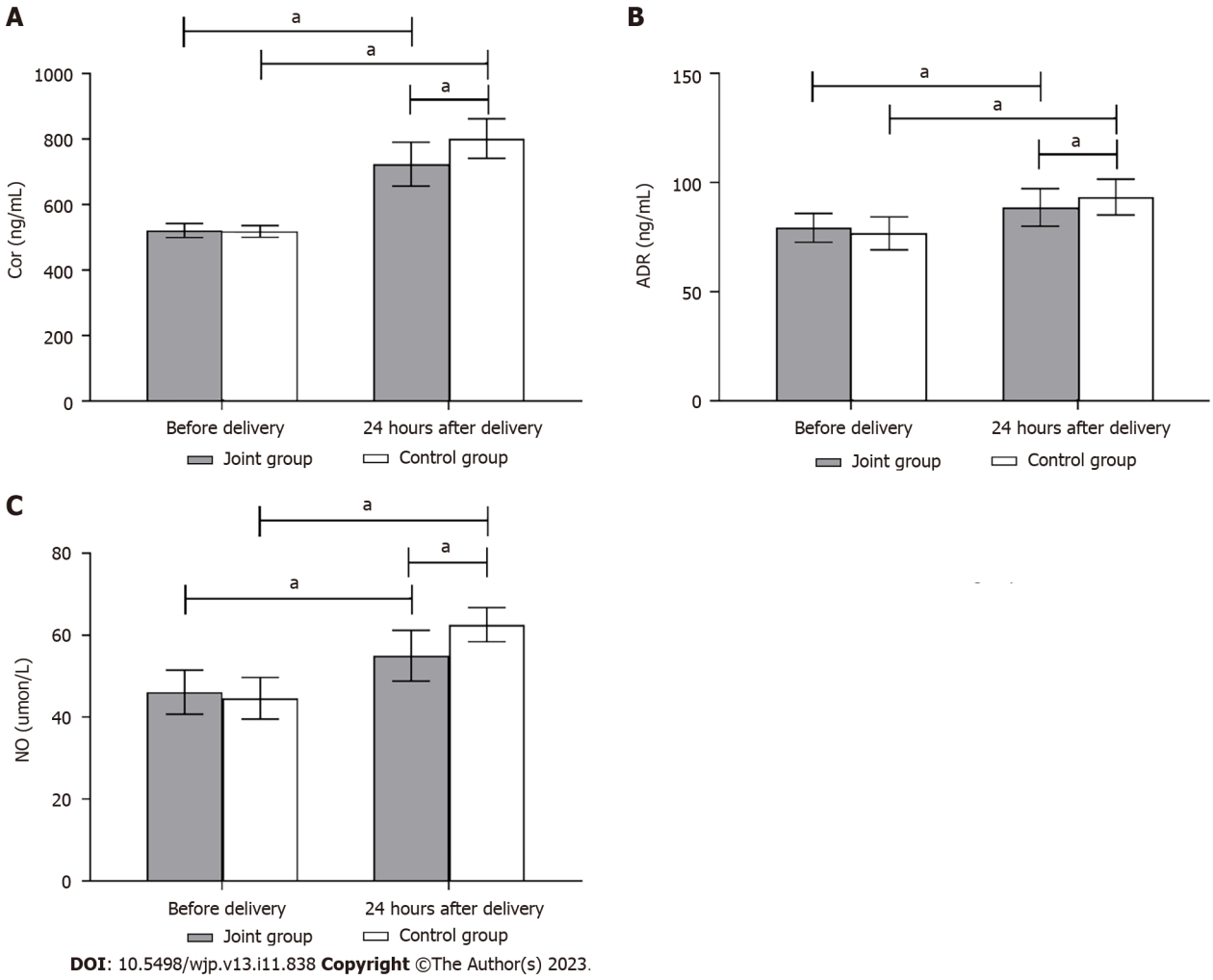

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Figure 6 Comparison of stress indices between the two groups. A: Comparison of cortisol value between the two groups; B: Comparison of adrenaline value between the two groups; C: Comparison of nitric oxide value between the two groups. $^{a}P < 0.05$, comparison with the joint group. Cor: Cortisol; ADR: Adrenaline; NO: Nitric oxide.

CONCLUSION

Combined spinal-epidural anesthesia for women during natural labor can reduce anxiety, ease pain, shorten the labor time, and reduce the postoperative stress level of the body, but did not result in a motor block. This study shows that, in addition to improving the method of anesthesia, prenatal education should also be carried out. By fully providing knowledge on labor and labor pain, prenatal education can help parturients understand how to judge labor pain, which is conducive to improving continuous muscle tension and enhancing the analgesic effect for painless labor.

ARTICLE HIGHLIGHTS

Research background

The background of this study is that the rate of natural childbirth is increasing, the rate of cesarean section is decreasing, and anesthesia and analgesia in natural childbirth are getting more and more clinical attention. The significance of this study is to explore new methods of anesthesia and analgesia in natural childbirth.

Research motivation

The main topic of this study is anesthesia and analgesia for natural parturients, and it is necessary to explore more effective anesthesia and analgesia methods for natural parturients. The significance of this study is to confirm the effectiveness of combined spinal-epidural anesthesia in the analgesia of women in natural childbirth, and encourage clinical teams to continue to explore more effective analgesia methods for women in natural childbirth.

Research objectives

The purpose of this study was to compare the analgesic effect of different analgesic methods on women in natural childbirth, and to observe the analgesic advantage of combined spinal-epidural anesthesia on women in natural childbirth. It was found that the combined spinal-epidural anesthesia can effectively improve the labor pain, shorten the labor process, relieve the bad mood and reduce the postoperative stress of the parturients. To provide a new reference for the analgesia of parturients in clinical natural labor in the future.

Research methods

In this study, the pregnant women were divided into two groups by randomized control method, and the general data, pain degree, newborn condition, self-efficacy, umbilical artery blood gas analysis index, stress index and movement blocker complications of the two groups were statistically analyzed by independent sample *t* test, paired sample *t* test and χ^2 test.

Research results

Combined spinal-epidural anesthesia has a more significant effect on the improvement of labor pain in women with natural delivery, with significant improvements in labor pain, cesarean section rate, blood loss, adverse emotions, stress reaction and other aspects, providing a new analgesic method for women with natural delivery. Further large-scale studies are needed to verify the effectiveness of this method.

Research conclusions

The bad mood of natural childbirth women can affect the pain threshold of women, making them more sensitive to pain, and pain strengthens the bad mood of women, affecting childbirth. Therefore, we should pay attention to the influence of analgesic methods on maternal bad mood. Combined spinal-epidural anesthesia has good analgesic effect on parturients in natural labor.

Research perspectives

Natural childbirth women should not only consider the outcome of childbirth, but also pay attention to the personal state of the mother during childbirth. Future research aims to further explore the effects of analgesia on maternal adverse mood and stress response.

FOOTNOTES

Author contributions: Cai L and Cao S initiated the project and designed the experiment; Jiang JJ conducted clinical data collection; Cai L and Jiang JJ performed postoperative follow-up and recorded data; Wang TT conducted a number of collation and statistical analysis; Cai L wrote the original manuscript; Cao S revised the paper; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Clinical application of multidisciplinary team- and evidence-based practice project in gynecological patients with perioperative hypothermia

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Abstract

BACKGROUND

Perioperative hypothermia (PH) negatively affects the physical and mental health of patients to varying degrees. Currently, there is no effective multidisciplinary team (MDT) intervention for gynecological patients with PH.

AIM

To apply the best evidence on the prevention and management of PH in gynecological patients, improve the quality of perioperative evidence-based care based on treatment by an MDT for gynecological patients and analyze the effect of MDT- and evidence-based practice (EBP) projects on the psychological status and cognitive function of gynecological patients with PH.

METHODS

Under the guidance of knowledge translation and combined with the opinions of involved stakeholders and clinical experts, the best evidence for PH prevention and management in gynecological patients was selected and adjusted to suit the practice setting. Based on the evidence, the practice plan was developed, and the MDT intervention was carried out in the preoperative ward, the preoperative preparation room, the intraoperative operating room, the postanesthesia care unit, and the 24-hour postoperative gynecological ward through the EBP program. The incidence of hypothermia, the nurses' awareness, the implementation rate of examination indicators, and the thermal comfort level, psychological status and cognitive function of patients were compared before and after the implementation of the program.

RESULTS

The incidence of PH in gynecological patients decreased from 43.33% to 13.33% after the implementation of the scheme. The implementation rate of examination

indicators 6-10, 12, 14, 16-18, 21, and 22 reached 100%, and that of other indicators was above 90%, except for examination indicators 5 and 13, which was 66.67%; the indices were significantly improved compared with the baseline (before evidence application) ($P < 0.05$). The score of nurses' awareness of PH prevention and management in gynecological patients increased from 60.96 ± 9.70 to 88.08 ± 8.96, and the difference was statistically significant ($P < 0.001$). The total score of the perioperative thermal comfort level of patients undergoing gynecological surgery was 27.97 ± 2.04, which was significantly increased compared with the score of 21.27 ± 1.57 observed by researchers at baseline ($P < 0.001$). The perioperative Hamilton Depression Scale and Hamilton Anxiety Scale scores of patients undergoing gynecological surgery decreased from 15.03 ± 3.16 and 13.93 ± 2.64 to 4.30 ± 1.15 and 3.53 ± 0.78, respectively, with statistically significant differences ($P < 0.001$). The perioperative Montreal Cognitive Assessment Scale score of the gynecological surgery patients increased from 23.17 ± 1.68 to 26.93 ± 1.11, also with statistical significance ($P < 0.001$).

CONCLUSION

MDT-based EBP for PH prevention and management in gynecological patients during the perioperative period can standardize nursing operations, improve nurses' awareness and behavioral compliance with gynecological hypothermia management, and reduce the occurrence of PH in gynecological patients while playing a positive role in reducing patients' negative emotions and enhancing their cognitive function.

Key Words: Hypothermia; Gynecology; Evidence-based care; Knowledge translation; Multidisciplinary team

Core Tip: At present, there is a lack of effective measures for perioperative hypothermia (PH) management in gynecological patients in China. This study verified the effectiveness of evidence-based practice project based on multi-disciplinary team in PH management of gynecological patients from the aspects of incidence of hypothermia, nurses' awareness, implementation rate of examination indicators, and the thermal comfort level, psychological status and cognitive function of patients.

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INTRODUCTION

Perioperative hypothermia (PH) refers to the phenomenon in which the body's core temperature is lower than 36 °C for various reasons in surgical patients[1] and has a high incidence. PH can delay the action time of anesthetic drugs, trigger unexpected events such as respiratory depression, vomiting and chills, and increase postoperative cardiovascular system complications, postoperative infection risk, coagulation dysfunction and other adverse consequences[2], prolonging the hospitalization time of surgical patients, increasing their hospitalization medical expenses and economic burden, and reducing social satisfaction[3]. Due to preoperative transfer, intraoperative anesthesia, the use of large amounts of flushing fluid, and the placement of patients in special positions, the incidence of PH in gynecological patients in China ranges from 31.3% to 65%[4,5], which is high, and the incidence in postanesthesia care units (PACUs) reaches 22.0%[6], necessitating improvement. The prevention and management of PH in gynecological patients is the responsibility of the multidisciplinary team (MDT)[7]. At present, the foreign practice guidelines and evidence summary on PH prevention and management are relatively comprehensive and mature. In contrast, although there are relevant studies and evidence on PH in China, none of them have been carried out according to the characteristics of gynecological patients, nor have they been effectively applied to clinical practice in China, resulting in a substantial difference between practice and evidence. In addition, there is no MDT intervention to improve the status quo of PH in patients. All these factors can explain the high incidence of PH in gynecological patients in China.

Knowledge translation (KT) refers to studying how to apply research evidence or clinical practice guidelines based on research evidence to clinical practice. The Knowledge-to-Action (KTA) framework, the most commonly used in KT theoretical frameworks, divides the KT process into knowledge creation and knowledge application, promoting the synthesis, dissemination and application of knowledge. The KT framework is a dynamic process through which knowledge producers (*i.e.*, researchers) and knowledge applicators (*i.e.*, practitioners) are integrated in a cooperative and interactive manner, reflecting a complete cycle from knowledge creation to application and providing a clear conceptual framework for the translation of knowledge into practice[8]. The application of an MDT under the guidance of KT may be of great help to the management of PH in gynecological patients. The MDT model of diagnosis, treatment and care has been shown to be one of the important models in medicine worldwide, which emphasizes patient-centered, curative effect-oriented, and evidence-based medicine to provide patients with all-round, personalized, refined, effective and

reasonable medical services[9]. MDT management has been shown to effectively improve the quality of life of patients with gynecological malignancies[10], promote their rapid recovery[11], and enhance the comprehensive ability of gynecological nurses[12]. To effectively prevent and manage the occurrence of PH in gynecological patients, the MDT-based evidence-based practice (EBP) project applies the best evidence scheme for the prevention and management of PH in gynecology, providing new ideas for solving the problem of PH in gynecological patients.

MATERIALS AND METHODS

Presentation of clinical problems

Based on a literature review and clinical practice, the clinical question "How can the incidence of PH be reduced in gynecological patients?", was identified and transformed into evidence-based problems according to the Population, Intervention, Control, and Outcome approach: (1) Population: Adult patients (≥ 18 years old) who underwent gynecological surgery (laparoscopy/hysteroscopy/Laparotomy) for 2 h or more; (2) Intervention: Prevention and management strategies of unplanned PH; (3) Control: Clinical routine nursing measures; and (4) Outcome: The implementation rate of examination indicators, nurses' awareness scores, incidence of hypothermia in gynecological patients, standardized procedures for PH prevention and management in gynecological patients, and psychological status and cognitive function of gynecological patients.

Construction of an evidence-based group

The team consisted of 9 members, including 2 operating room head nurses, 1 head nurse in the anesthesiology department, 1 head nurse in the gynecology department, 3 floor nurses, and 2 postgraduate students. Among them, the operating room head nurses were responsible for the overall research design and guidance; the postgraduates were responsible for evidence extraction, baseline review, data collection and analysis; and the remaining team members were responsible for nurse training, organization and coordination, and quality supervision.

Evidence acquisition

In this study, relevant clinical practice guidelines, expert consensus, evidence summaries and systematic reviews were retrieved from databases such as PubMed/Medline, JBI's Evidence-based Practice Database, the Cochrane Library, National Institute of Health and Care Excellence, Registered Nurses Association of Ontario, OVID, Science Direct, Association of the Scientific Medical Societies in Germany (AWMF), Association of Operating Room Nurses, China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, and Chinese BioMedical Literature Database from 2000 to April 2021. Of the 592 documents retrieved, 7 articles were included after reading the abstracts and full texts and evaluating the literature quality, including 2 guidelines[13,14], 2 expert consensuses[2,15], and 3 systematic reviews[16-18]. For the guidelines included, the quality was quantitatively evaluated using the Appraisal of Guidelines for Research and Evaluation instrument II[19], and the results are shown in Table 1. The Assessment of Multiple Systematic Reviews score[20] was used for quality assessment of the systematic reviews included, with the results presented in Table 2. For expert consensus, the quality was assessed by referring to JBI's critical appraisal tools[21]; the evaluation results of all the other items of the two articles were "Yes" except Item 6, "Are there any inconsistencies between all the proposed opinions and previous documents?" The research design of the included articles was complete, and the overall quality was high, which met the inclusion criteria. A total of 26 pieces of relevant evidence were obtained through the included studies, as shown in Table 3.

Selection of evidence suitable for clinical settings

The KTA model emphasizes the appropriate selection of evidence to suit specific clinical scenarios[8] and the adjustment of evidence with the input of stakeholders. In this study, 16 nurses and doctors from different departments (operating room, department of gynecology, and department of anesthesiology) with different academic qualifications and working years were selected as stakeholders by purposive sampling to select evidence suitable for clinical settings. Then, the stakeholders selected and adjusted evidence from the aspects of applicability, suitability, effectiveness and clinical significance. According to the opinions of the involved stakeholders, the applicability of heating humidification for oxygen inhalation was not considered feasible, so the evidence "to provide heated and humidified oxygen therapy for patients" was deleted (see Table 4 for the final included evidence).

Identification of gaps between evidence and clinical practice

To introduce evidence into clinical practice, this study evaluated the readiness of EBP. According to the evidence introduced into clinical practice, a total of 23 examination indicators were used as the evaluation criteria to investigate the current status of evidence application for PH prevention and management in gynecological patients in the pilot wards. The research subjects and examination methods are shown in Table 4. The review was jointly completed by the researcher and another member of the research team. Before the review, the examination contents and evaluation methods were further confirmed with the research team to ensure consistency. Except for indicators 1, 10, 12, 18, and 19, the implementation rate of other indicators was less than 50%, with the implementation rate of indicators 4 and 22 even being 0, suggesting the need to improve the completion of evidence implementation by medical staff. Therefore, this study investigated the awareness of relevant medical staff in the pilot wards on the prevention and management of PH in gynecological patients. A self-designed questionnaire was developed based on the evidence content to assess nurses' knowledge

Table 1 Quality evaluation results of the included guidelines

Ref.	Percentage of standardization in various fields						Number of domains ≥ 60% (*n*)	Number of domains ≥ 30% (*n*)	Recommended level
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence			
Torossian *et al*[13]	100	88.89	79.17	100	68.75	62.5	6	6	A
Hooper *et al*[14]	88.89	52.78	62.5	80.56	43.75	20.84	3	5	B

Table 2 Quality evaluation results of the included systematic reviews

Indicators	Galvão *et al* [17]	Moola and Lockwood [18]	Wang and Mao [16]
Was an "a priori" design provided?	Yes	Yes	Yes
Was there duplicate study selection and data extraction?	Yes	Yes	Yes
Was a comprehensive literature search performed?	Yes	Yes	Yes
Was the status of publication used as an inclusion criteria, such as grey literature?	No	Yes	No
Was a list of studies provided?	Yes	Yes	Yes
Were the characteristics of the included studies provided?	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes
Was the likelihood of publication bias assessed?	No	No	Yes
Was the conflict of interest stated?	Yes	Yes	No

level (20 items for hypothermia identification, assessment, prevention, treatment and health education domains, with 2.5 points for each item) and practice level (10 items for the aspects of attitude and awareness of the prevention and management of PH in gynecological patients, with 5 points for each item), with a total score of 100 points. A total of 49 nurses in the pilot wards were enrolled, and the inclusion criteria were as follows: (1) Working in the department for more than 2 years; and (2) Voluntary participation in this study. The awareness of nurses regarding PH prevention and management in gynecological patients was 60.96 ± 9.70 points, which was at the medium level.

Development of MDT-based EBP project

Based on the evidence content, the investigation results of the implementation of the examination indicators in the pilot wards and the awareness of the associated medical staff, as well as the "Promoting Action on Research Implementation in Health Services Integrated Framework (i-PARIHS)"[22], semistructured interviews were conducted among nurses from different wards with different seniority levels to identify barriers and facilitators for the implementation of the protocol. After the formulation of action strategies, the evidence-based team developed an EBP project for PH prevention and management in gynecological patients, compiled a manual of relevant surgical education and knowledge, developed a thermal comfort rating scale, and unified the comprehensive thermal insulation methods and procedures for gynecological surgery patients. After the formation of the scheme, the evidence-based team discussed the comprehensiveness and clinical feasibility of the scheme item by item with the hospital management team members and nine experts with extensive perioperative nursing experience in gynecology, and the program was unanimously recognized.

EBP program application and effect evaluation

Practice site: The EBP program of this study was conducted in the operating room and gynecology and anesthesiology departments of a grade III-A hospital in Sichuan Province, with a total of 49 nurses participating (see 1.5 for the inclusion criteria).

Implementation of the EBP project: The EBP project was implemented from August to October 2021. The KTA model notes that to promote changes in practice, effective action strategies should be developed according to the barriers to evidence application. This study drew on the i-PARIHS framework to analyze the barriers and facilitators in the application of evidence for the prevention and management of PH in gynecological patients in pilot wards, with the

Table 3 Contents of the best evidence

Stage	Evidence
Preoperative ward	To educate patients on thermal insulation and matters needing attention before surgery
	To measure and record the patient's axillary temperature before surgery
	To actively warm patients whose body temperature is below 36°C to 36°C and keep the patient warm during transfer
Preoperative preparation room	To assess the risk factors for hypothermia in patients
	To use a temperature monitoring equipment to measure and record the patient's body temperature before anesthesia induction
	To preheat 10-30 min before anesthesia induction
	To use carbon fiber heating wire to actively and continuously warm patients with body temperature below 36°C to above 36°C
	To maintain the operating room temperature no less than 24°C, and to lower the temperature only when active heating is established
Intraoperative operating room	To adopt an effective comprehensive thermal insulation strategy after anesthesia and maintain the axillary temperature at least 36.5°C
	To expose the surgical area and cover the rest for thermal insulation
	The infusion pipeline is continuously heated to 37°C if the intravenous infusion volume is more than 500ml.
	To heat the washing solution with a thermostatic chamber to 38-40°C
	To perform continuous intraoperative monitoring and recording every 15 min
	To evaluate intraoperative risk factors and hypothermia symptoms and signs
Postanesthesia care unit	To measure the body temperature and record it every 15 min. Passive insulation is adopted if there is no hypothermia. Monitoring site: armpit
	To adjust the PACU ambient temperature to 24°C
	To evaluate the patient's thermal comfort level
	To actively warm patients whose body temperature is below 36°C to above 36°C
	To heat the intravenous fluids
	To provide heated and humidified oxygen therapy for patients
	To transfer the patient out of PACU only when her body temperature is ≥ 36°C
24-hour postoperative gyneco-logical ward	To measure, monitor and record the body temperature every 4 h
	To cover to keep warm
	To educate family members thermal insulation methods: blankets, socks, clothes, raising the ambient temperature, hot water, *etc*.
	To continuously and actively warm patients below 36°C until they feel warm and comfortable, and to monitor and record every 30 min
	To evaluate the patient's thermal comfort level
	To pay close attention to patients' psychological changes, perceive their potential negative emotions such as anxiety and depression, and give timely relief and comfort
	To patiently answer any problems that may cause psychological distress to patients, and help them establish a positive attitude

PACU: Postanesthesia care unit.

results presented in Table 5. According to the barriers and the actual situation in the wards, the following action strategies were developed for the smooth implementation of the EBP project.

Effect evaluation: The research participants consisted of 16, 13, and 20 nurses from the gynecological operating room, anesthesiology department, and gynecology department, respectively, as well as 60 patients undergoing gynecological surgery (inclusion criteria: Age ≥ 18 years; operation time ≥ 2 h; good cognitive and responsive skills; voluntary participation in this study). The effect of the EBP project was evaluated by a controlled before-and-after trial among nurses and a nonconcurrent control trial among patients.

Table 4 Relationship between evidence, practice protocol related documentation and examination indicators

Stage	Evidence suitable for clinical scenarios	Practice protocol related documentation	Examination indicators	Examination objectives and methods
Preoperative ward	To educate patients on thermal insulation and matters needing attention before surgery	Manuals and videos of perioperative health education (patient edition)	The operating room has propaganda materials on hypothermia prevention and management	Department: Document consultation
			Checking the preoperative follow-up sheet of gynecological surgery patients	Medical staff: Document consultation and observation
	To measure and record the patient's axillary temperature before surgery	Surgical patient handover/transfer proforma	Checking the surgical patient handover/transfer proforma	Medical staff: Document consultation and observation
	To actively warm patients whose body temperature is below 36°C to 36°C and keep the patient warm during transfer	Hypothermia emergency procedures	The operating room has a hypothermia emergency process to ensure continuous heat preservation during patient transfer	Medical staff: Document consultation and observation
Preoperative operating room	To assess the risk factors for hypothermia in patients	Hypothermia risk factor evaluation sheet	The operating room has an evaluation sheet to evaluate the risk factors of hypothermia in patients	Operating Room: document consultation
	To use a temperature monitoring equipment to measure and record the patient's body temperature before anesthesia induction	Procedure for the use of temperature monitoring equipment	Before anesthesia induction, a temperature monitoring equipment is used for patients with operation duration of 2h or longer	Medical staff: Observation and document consultation
	To actively warm patients whose body temperature is below 36°C to above 36°C	Active heat preservation methods for hypothermia patients	Effective warming strategies are taken for hypothermia patients	Medical staff: Observation and document consultation
	To preheat 10-30 min before anesthesia induction	Pre-heat preservation methods	10-30 min of pre-heat preservation is performed on gynecological patients before anesthesia induction	Medical staff: Observation
	To maintain the operating room temperature no less than 24°C, and to lower the temperature only when active heating is established	-	The operating room ambient temperature is adjusted to 24°C and above before surgery	Medical staff: Observation
Intraoperative operating room	To adopt an effective comprehensive thermal insulation strategy after anesthesia and maintain the axillary temperature at least 36.5°C	Intraoperative comprehensive thermal insulation strategies (active and passive thermal insulation, blood transfusion and infusion warming, continuous dynamic monitoring of body temperature, *etc.*)	According to the probability of hypothermia in gynecological patients during operation, a corresponding comprehensive heat preservation strategy is selected to maintain the axillary temperature of the patient at least 36.5°C	Medical staff: Observation, document consultation
	To expose the surgical area and cover the rest for thermal insulation	-	The surgical area is exposed and the rest is covered for thermal insulation	Medical staff: Observation
	To warm the intravenous fluid or blood transfusion with a warming device to 37°C if the amount was ≥ 500 mL	Procedure for the use of infusion pipeline heating instrument	The infusion pipeline was warmed for those with a intravenous fluid or blood transfusion volume ≥ 500 mL	Medical staff: Observation
	To heat the intraoperative washing solution with a thermostatic chamber to 38-40°C	-	The washing solution is used at 38-40°C	Medical staff: Observation
	To continuously monitor and record the patient's body temperature once every 30 min intraoperatively, and to record it once every 15 min during recovery from anesthesia	-	The body temperature is continuously monitored and recorded on time intraoperatively	Medical staff: Observation, document consultation
	To evaluate hypothermia symptoms and signs during the operation	Evaluation methods of symptoms and signs of hypothermia in patients during operation	The patient is observed for symptoms and signs of hypothermia during the operation	Medical staff: Observation
PACU	To measure the body temperature and record it every 15 min. Passive	Active insulation methods and temperature handover record for	The patient's temperature is measured and the hypothermia patients are	Medical staff: Observation,

	thermal insulation is adopted for those without hypothermia, and active thermal insulation is taken to above 36°C for those below 36°C	hypothermia patients	warmed effectively, and the temperature handover record is established	document consultation
	To adjust the PACU ambient temperature to 24°C	-	The PACU temperature is adjusted to 24°C and above	Medical staff: Observation
	To send the patient back to the ward when the body temperature is not lower than 36°C	-	The patient is transferred out from the PACU only when the body temperature is ≥ 36°C	Medical staff: Observation, document consultation
24-hour postoperative gynecological ward	To monitor and record the patient's axillary temperature every 4 h	-	The patient's axillary temperature is measured and recorded every 4 h	Medical staff: Observation, document consultation
	To cover to keep warm	-	The patient is covered to keep warm	Medical staff: observation
	To teach the patient's family how to keep warm effectively	Health education handbook	The patient's family members' are informed of effective thermal insulation methods	Medical staff: Observation and questioning
	To continuously and actively warm patients below 36°C until they feel warm and comfortable, and to monitor and record every 30 min	Active heat preservation methods for hypothermia patients	The hypothermia patients are continuously and actively warmed, with their body temperatures monitored and recorded every 30 min	Medical staff: Observation, document consultation
	To evaluate the patient's thermal comfort level	Thermal comfort rating scale	The patient's thermal comfort level is assessed	Medical staff: Document consultation

PACU: Postanesthesia care unit.

Table 5 Barriers and action strategies for prevention and management of hypothermia in patients

Serial number	Obstacle	Action strategy
1	Nurses lack relevant knowledge and awareness of perioperative hypothermia management of gynecological patients	To hold special training to explain relevant knowledge to nurses with PPT combined with nursing knowledge handbook, and to explain various procedures and nursing norms through on-site demonstration and watching operation videos. To ensure that nurses in the operating room, anesthesiology department and gynecology department receive knowledge training on hypothermia prevention at least once every six months, and to assess them for knowledge and practice at least once a year after training
2	The contents of health education on the day before surgery vary greatly and lacks gynecological expertise	To formulate a preoperative education manual of gynecology specialty, and to push the preoperative education video for gynecological patients by WeChat official account
3	The lithotomy position is mostly commonly used posture in gynecological surgery, resulting in inadequate ankle and foot warmth. In addition, there is a lack of special thermal insulation equipment for the lithotomy position	To purchase lithotomy position-dedicated strip-shaped inflatable heating blankets, wrap the patient's legs with cotton pads, and use sterile leg covers to meet the warm-keeping requirements of patients undergoing surgery in the lithotomy position
4	There are communication barriers among multi-department nurses on the prevention and management of perioperative hypothermia in gynecological patients	To establish a perioperative hypothermia prevention and management group led by the head nurses who also play a key role in the practice reform, with operating room gynecological specialists, anesthesiology nurses, gynecological nurses as the team members and the head nurses of the three departments as the group leaders. To establish a WeChat exchange group to remind, supervise and control the quality in the preoperative ward, preoperative preparation room, intraoperative operating room and postoperative PACU. To listen to the feedback and suggestions of nurses and patients during field observation, and adjust and optimize the nursing process. The head nurse should report the practice changes to the evidence-based practice group every month, so as to discuss, analyze and solve the problems that arise
5	There is a lack of corresponding evaluation tools	To introduce the intraoperative hypothermia risk prediction model calculation software constructed by Professor Huang Yuguang to evaluate the hypothermia risk of patients, and to explain the checked contents. To self-develop a thermal comfort scale, and conduct unified training for medical staff

PACU: Postanesthesia care unit; PPT: Power point.

Outcome measures: (1) The implementation rate of examination indicators was as follows: The evidence suitable for clinical situations was converted into measurable and easy-to-assess quality examination indicators. If the examination indicators were correctly executed, they were marked with "√". Unimplemented or incorrectly implemented indicators were marked with "×". The percentage of correct implementations was calculated as the percentage of the number of correct implementations out of the total number of implementations; (2) The incidence of PH was evaluated as follows: The incidence of PH in 30 gynecological patients from April to June 2021 and another 30 gynecological patients from October 2021 to December 2021 was statistically analyzed; (3) The awareness level of nurses (gynecological operating room, anesthesiology department, and gynecology department) regarding PH prevention and management in gynecological patients was evaluated as follows: A self-designed questionnaire based on evidence content was used for assessment (see 1.5 for details); (4) The thermal comfort level of gynecological patients was investigated as follows: The operating room, PACU and gynecological ward patients were scored by the Visual Analog Scale. The scale has 10 items, with 10 points each and a full score of 30; (5) Psychological status was evaluated as follows: Patients' depression and anxiety were evaluated by the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA), respectively, whereby the HAMD score range was 0-68 and the HAMA score range was 0-56, both of which were directly proportional to depression and anxiety; and (6) Cognitive function was analyzed as follows: Patients' cognitive function was evaluated with the Montreal Cognitive Assessment Scale (MoCA; score range: 0-30). A score of 26 was considered normal, and a score less than 26 was indicative of cognitive function decline; in addition, the score was increased by 1 point if the patient's years of schooling was less than 12 years.

Data collection methods: Baseline review data were collected from April 2021 to June 2021, and data collection and analysis after program application were carried out from October 2021 to December 2021. A researcher followed up and observed the implementation of examination indicators and the occurrence of hypothermia on a daily and patient-by-patient basis and recorded it truthfully. (1) Document consultation: For indicators 1-7, 10, 14, 16, 18-19, and 22-23, the rules and regulations of the department, the relevant processes and the training records were checked; (2) Observation and questioning: For indicators 2-4 and 6-22, the "Checklist for Prevention and Management of Unplanned Hypothermia in Gynecological Surgery Patients" was formulated, and the nurses' implementation of the best evidence was evaluated through data analysis after clinical implementation; and (3) Questionnaire survey method: Based on the implementation of the examination indicators, a questionnaire on nurses' knowledge and practice was designed and prepared and distributed by the head nurse to the nurses to complete.

Statistical methods: SPSS 20.0 statistical software and Excel software were used for data entry and analysis. The quantitative data that conformed to a normal distribution are described by means ± standard deviations, and between-group comparisons were made by the *t* test; count data are described as frequencies and percentages, and chi-square tests were performed to identify differences between groups. All analyses relied upon a $P < 0.05$ statistical significance criterion.

RESULTS

General information

A total of 49 nurses (16, 13, and 20 nurses in the gynecological operating room, anesthesiology department, and gynecology department, respectively), including 44 females and 5 males aged 22-50 (32.1 ± 5.9) years, were investigated before and after the application of this scheme. Most of the nurses had bachelor's degrees (87.76%) and professional titles (67.35%). Thirty patients each were included before and after evidence application, and no significant intergroup differences were identified in terms of age, sex, length of hospital stay, education level, occupation, payment method of medical expenses, or operation duration ($P > 0.05$).

Incidence of hypothermia

The incidence of hypothermia among gynecological perioperative patients decreased from 43.33% to 13.33% after the application of the scheme, with statistical significance ($\chi^2 = 12.381$, $P < 0.001$).

Implementation rate of examination indicators

After the application of evidence, the implementation rate of examination indicators 6-10, 12, 14, 16-18, and 21-22 reached 100%; in addition to indicators 5 and 13 with an implementation rate of 66.67%, the implementation rate of other indicators was 90% or above. Except for indicators 10, 12, and 18, whose implementation rate had been 100% before evidence application, all the other indicators were significantly improved after evidence application ($P < 0.05$) (Table 6).

Nurses' awareness of PH prevention and management in gynecological patients

After the application of the EBP project, the nurses' awareness of PH prevention and management in gynecological patients increased from 60.96 ± 9.70 to 88.08 ± 8.96, with a statistically significant difference ($t = -29.866$, $P < 0.001$).

Perioperative thermal comfort level of patients undergoing gynecological surgery

The total score of the perioperative thermal comfort level of gynecological surgery patients was 27.97 ± 2.04 after the application of the EBP project, which was statistically significant compared with the score of 21.27 ± 1.57 established by

Table 6 Comparison of nurses' implementation of examination indicators before and after application of the evidence-based program

Examination indicators	Before evidence application (n = 30)			After evidence application (n = 30)			X^2	P value
	Implemented	Unimplemented	Implementation rate (%)	Implemented	Unimplemented	Implementation rate (%)		
Indicator 1	16	14	53.33	28	2	93.33	12.273	< 0.001
Indicator 2	15	15	50.00	29	1	96.67	20	< 0.001
Indicator 3	12	18	40.00	28	2	93.33	19.2	< 0.001
Indicator 4	0	30	0.00	27	3	90.00	49.091	< 0.001
Indicator 5	7	23	23.33	20	10	66.67	11.38	0.001
Indicator 6	15	15	50.00	30	0	100.00	20	< 0.001
Indicator 7	12	18	40.00	30	0	100.00	25.714	< 0.001
Indicator 8	15	15	50.00	30	0	100.00	20	< 0.001
Indicator 9	11	19	36.67	30	0	100.00	27.805	< 0.001
Indicator 10	29	1	96.67	30	0	100.00	1.017	0.313
Indicator 11	6	24	20.00	27	3	90.00	29.697	< 0.001
Indicator 12	28	2	93.33	30	0	100.00	2.069	0.15
Indicator 13	7	23	23.33	20	10	66.67	11.38	0.001
Indicator 14	3	27	10.00	30	0	100.00	49.091	< 0.001
Indicator 15	4	26	13.33	28	2	93.33	38.571	< 0.001
Indicator 16	14	16	46.67	30	0	100.00	21.818	< 0.001
Indicator 17	11	19	36.67	30	0	100.00	27.805	< 0.001
Indicator 18	30	0	100.00	30	0	100.00	-	-
Indicator 19	21	9	70.00	29	1	96.67	32.308	< 0.001
Indicator 20	12	18	40.00	28	2	93.33	19.2	< 0.001
Indicator 21	10	20	33.33	30	0	100.00	30	< 0.001
Indicator 22	0	30	0.00	30	0	100.00	60	< 0.001

researchers before the intervention (t = 13.693, P < 0.001).

Perioperative psychological status of patients undergoing gynecological surgery

The total score of the perioperative HAMD of gynecological surgery patients was 4.30 ± 1.15 after the application of the EBP project, which was statistically significant compared with the score of 15.03 ± 3.16 established by researchers before the intervention (t = 17.500, P < 0.001); the total HAMA score decreased from 13.93 ± 2.64 before the intervention to 3.53 ± 0.78 after the intervention, with statistical significance (t = 20.713, P < 0.001).

Perioperative cognitive function of patients undergoing gynecological surgery

The total MoCA score among gynecological surgery patients was 26.93 ± 1.11 after the application of the EBP project, which was statistically significant compared with the score of 23.17 ± 1.68 established by researchers before the

intervention (t = 10.226, P < 0.001).

DISCUSSION

The EBP project based on an MDT was scientific and feasible

A top-down literature search according to the "6S" retrieval model was conducted in this study, as well as rigorous study screening and quality evaluation. The quality evaluation results of the included documents were all high, which ensured the reliability of the evidence sources. To make the summarized evidence of MDT nursing of gynecological patients at different stages of the perioperative period feasible, appropriate, effective and clinically significant, this study followed the FAME principle and invited relevant stakeholders (clinical practitioners) from gynecology, anesthesiology and the operating room to participate in the evidence selection process, which enhanced the clinical practitioners' recognition of the evidence[23]. In addition, relevant experts were invited for consultation, and the clinical experience of clinical decision-makers, managers and practitioners was combined with the clinical evidence application sites, such as the operating room, gynecology and anesthesiology, so that the examination indicators were practical in clinical work. Moreover, based on continuous quality improvement advocated by the KT model and drawing on the i-PARIHS framework (which takes into account all issues that need to be considered, evaluated and planned in the process of evidence application and has been effectively applied in clinical practice as a theoretical framework to guide quality improvement and for the identification of prestudy barrier factors and facilitating factors[22]), this study analyzed the barriers and facilitators in the application of evidence related to the prevention and management of PH in gynecological patients in pilot wards. After determining the major barriers, action strategies were drawn up, and evidence-based intervention programs were formed. The whole process is standardized and scientific, which makes the EBP project scientific and feasible.

The MDT-based EBP project improved the implementation rate of examination indicators and enhanced nurses' awareness of hypothermia prevention and management

Based on the KT model, this EBP project transformed the evidence into clinical practice, formulated an intervention plan for PH prevention and management suitable for local gynecological surgery patients, and filled the relevant vacancies in the pilot operating room. Through the analysis of barriers, tailored action strategies were formed, contributing to the increase in the scores of ward nurses, operating room nurses and anesthesia nurses on PH prevention and management in gynecological patients from 60.96 ± 9.70 to 88.08 ± 8.96 and the increase in the examination indicator implementation rate from 0-100% to 66.67-100%, which was significantly improved compared with the values before evidence application (P < 0.05). This suggests that the EBP project enhanced the awareness of hypothermia prevention and management among nursing staff, especially gynecological nurses, and that most of the evidence was well applied in clinical practice. This may be related to the construction of practice plans, the implementation of action strategies and quality supervision, which clarified the job responsibilities and standardized the behavior of nurses, thus promoting changes in clinical practice, consistent with the results of a number of studies[24,25].

The EBP project based on an MDT reduced the incidence of PH in gynecological patients

The necessity and importance of the prevention and management of PH in surgical patients, an important part of operating room care, have been emphasized in the guidelines[13,14] when selecting the best evidence in this study. After the implementation of this EBP project, the incidence of PH in gynecological patients in the pilot wards decreased from 43.33% to 13.33%, and the score of perioperative thermal comfort level increased from 21.27 ± 1.57 to 27.97 ± 2.04, with statistical significance. It is suggested that the EBP project can effectively reduce the incidence of PH in gynecological patients and improve their thermal comfort level, similar to the findings of Xiao *et al*[26]. This may be related to the fact that this EBP project takes evidence-based evidence as the theoretical basis, implements patient-centered and multidisciplinary cooperation, and focuses on temperature management of gynecological patients throughout the perioperative period, including gynecology, operating room and PACU. The specific measures include giving health education about body temperature to patients and their families before and after surgery in gynecological wards; conducting preoperative hypothermia risk assessment and preinsulation in the operating room; using a lithotomy position-dedicated inflatable heating blanket during the operation according to the characteristics of commonly used lithotomy positions for gynecological patients, which can effectively cover the whole body of the patient with a better heating effect compared with the whole-body inflatable heating blanket in the supine position[27]; implementing comprehensive warm-keeping measures such as intravenous infusion and transfusion heating, lavage fluid heating and continuous body temperature monitoring; emphasizing continuous body temperature monitoring and passive thermal insulation when patients are in the PACU; performing temperature monitoring and active thermal insulation measures of abnormal hypothermia in the gynecological ward 24 h after surgery; and paying attention to the patient's thermal comfort level during the whole perioperative period. However, due to the short application time of evidence in this study and the small number of patients included, the effectiveness of this protocol needs validation through continuous application.

The EBP project based on an MDT improved the psychological status and cognitive function of gynecological patients during the perioperative period

In this study, the psychological status of gynecological patients during the perioperative period was evaluated by the HAMD and HAMA, and cognitive function was assessed by the MoCA. Before the implementation of the MDT-based

EBP project, gynecological perioperative patients suffered from varying degrees of negative emotions and cognitive impairment. Negative emotions such as anxiety and depression were significantly alleviated after the implementation of the MDT-based EBP project, and cognitive function was also significantly improved, mainly manifested in the significant reduction in HAMD and HAMA scores and the significant increase in MoCA scores. The above results suggest that the EBP project based on MDTs can effectively improve the psychological status and cognitive function of gynecological patients during the perioperative period. This may be attributed to the identification of potential psychological distress in perioperative gynecological patients and psychological interventions in the MDT-based EBP project. In addition to hypothermia prevention and thermal comfort intervention in the wards 24 h after surgery, the relevant members of the evidence-based team were also required to pay close attention to the psychological changes of patients and provide timely relief and comfort to minimize their negative emotions. At the same time, it is also necessary to give careful attention and patient answers to problems that may cause psychological distress to patients, which helps patients establish a positive psychological attitude and improve their compliance with relevant EBP steps. In the study of Meng *et al*[28], the application of an EBP project based on MDT to postpartum anxiety and depression also significantly reduced adverse mood and improved patients' nursing satisfaction, which supports our findings. Another study pointed out that the EBP project based on MDT can assist patients undergoing gynecological laparoscopic surgery with propofol and fentanyl to improve their mental health, similar to our research results[29]. Dai *et al*[30] also reported that evidence-based nursing interventions based on MDTs are beneficial for improving the cognitive function of patients in intensive care units, which is mainly reflected in significantly increased Mini-Mental State Examination scores and a reduced incidence of delirium after intervention, which is consistent with our research results. In this study, the improvement in cognitive function in gynecological perioperative patients by the MDT-based EBP project may be related to its effective reduction in the incidence of hypothermia.

MDTs facilitate the effective management of PH in gynecological patients

Munday *et al*[7] reported that intervention strategies based on the MDT model can maximize the effect of PH prevention and management. Drawing on the i-PARIHS framework, this study found that communication was blocked in the prevention and management of PH in gynecological patients among nurses from different departments. At present, there is a fault segmentation in the temperature management of patients in the operating room, gynecological ward and PACU, and patient transport and handover are neglected. To solve this obstacle, the EBP project established a multidisciplinary collaboration team led by nurses, clarified the division of team roles, detailed the professional responsibilities of the preoperative ward, preoperative preparation room, intraoperative operating room, postoperative PACU, and postoperative 24-hour gynecological ward in the prevention and management of hypothermia throughout the perioperative period of gynecological patients, and set up a WeChat communication group to ensure smooth and timely response of information among disciplines, thus promoting communication and cooperation among multiple disciplines, which was consistent with the research results of Shi *et al*[31]. In addition, the body temperature supervision mechanism and the overall quality control process led by the head nurses of the operating room, gynecology and anesthesiology departments were improved. Furthermore, the head nurses reported the practice changes to the evidence-based team monthly to allow for time identification of barriers and facilitators. Moreover, the evidence-based team conducted a quality inspection every quarter to solve problems such as nurses' inadequate assessment of hypothermia risk factors, insufficient supply of 38-40 °C irrigation solution during operations, and inadequate adjustment of ambient temperature to ensure reasonable, feasible and perfect implementation of all aspects and further promote the effective management of PH in gynecological patients. MDTs can integrate medical resources and lead patients to better rehabilitation outcomes [32].

The MDT-based EBP project needs further continuous improvement

The KTA model emphasizes the continuous use and consolidation of knowledge[8], that is, continuous quality improvement of the project after implementation and evaluation. The commonly used quality improvement models are PDCA circulation and quality control circles, which have been widely applied in medical and nursing fields and have achieved remarkable results in advocating medical and nursing quality improvement. In this study, the implementation rate of intraoperative temperature monitoring equipment use and intraoperative temperature monitoring every 15 min in gynecological surgery patients was 66.67% after the application of the EBP project, indicating the poor implementation of intraoperative body temperature monitoring and the need for further improvement. This is related to the use of wireless temperature monitoring equipment in the pilot operating room. This device can realize continuous monitoring of core temperature every minute, but there are some problems, such as a high cost of use, discontinuous temperature monitoring due to a weak Bluetooth signal during operations, and equipment failure, which makes some patients refuse to use temperature monitoring equipment, resulting in loss of temperature monitoring values. Patients who refuse to use wireless temperature monitoring equipment have to be monitored manually by visiting nurses every 15 min, which increases the nurses' workload and leads to the low implementation rate of nurses' norms. On the other hand, in this EBP project, although body temperature management of patients in the PACU was strengthened, there was a lack of thermal insulation equipment for patients with hypothermia. Studies have shown that using the modified inflatable thermal insulation quilt for patients with mild hypothermia has the same warming effect as the inflatable heating blanket, which can not only reduce costs but also be suitable for rewarming PACU patients with hypothermia. Therefore, the common quality improvement model can be combined in the future to further optimize PH prevention and management in gynecological patients.

CONCLUSION

This study focused on the high incidence of PH in gynecology. Guided by KT drawing on the best evidence and i-PARIHS framework and combined with the wishes of stakeholders and expert opinions, an EBP project based on an MDT was formulated and implemented, which effectively promoted the application of evidence, strengthened multidisciplinary cooperation, standardized the prevention and management of PH in gynecology, improved nurses' awareness, and effectively enhanced nursing quality. For gynecological patients during the perioperative period, this project lowered the incidence of PH and improved their thermal comfort level, psychological status and cognitive function. However, the implementation effect of some examination indicators was still not satisfactory, and relevant procedures and systems need further optimization. In the future, how to standardize the monitoring of patients' continuous body temperature during surgery needs further discussion.

ARTICLE HIGHLIGHTS

Research background

Perioperative hypothermia (PH) has varying degrees of negative effects on the physical and mental health of patients, and there is no effective multidisciplinary team (MDT) intervention for PH in gynecological patients.

Research motivation

Despite the comprehensiveness and maturity of the practice guidelines and evidence summaries on PH prevention and management in foreign countries, there is a lack of effective clinical practice for PH in gynecological patients in China, so it is necessary to conduct this analysis to fill in this gap.

Research objectives

To apply the best evidence on the prevention and management of PH in gynecological patients, to improve the quality of perioperative evidence-based care based on MDT treatment of gynecological patients, and to analyze the effect of MDT-based evidence-based practice (EBP) project on the psychological status and cognitive function of gynecological patients with PH.

Research methods

Under the guidance of knowledge translation and combined with the opinions of stakeholders involved and clinical experts, the best evidence for PH prevention and management in gynecological patients was selected and adjusted to suit the practice setting. Based on the evidence, the practice plan was developed, and the MDT intervention was carried out in the preoperative ward, the preoperative preparation room, the intraoperative operating room, the postanesthesia care unit, and the 24-hour postoperative gynecological ward through the EBP program. The incidence of hypothermia, the nurses' awareness, the implementation rate of examination indicators, and the thermal comfort level, psychological status and cognitive function of patients were compared before and after the program application.

Research results

The incidence of PH in gynecological patients decreased from 43.33% to 13.33% after the application of the scheme. The implementation rate of examination indicators 6-10, 12, 14, 16-18, 21, and 22 reached 100%, and that of other indicators was above 90% except for examination indicators 5 and 13, which was 66.67%; the indexes were significantly improved compared with the baseline (before evidence application), with statistically significance ($P < 0.05$). The score of nurses' awareness of PH prevention and management in gynecological patients increased from (60.96 ± 9.70) to (88.08 ± 8.96), and the difference was statistically significant ($P < 0.001$). The total score of perioperative thermal comfort level of patients undergoing gynecological surgery was (27.97 ± 2.04), which was statistically increased compared with the score of (21.27 ± 1.57) investigated by researchers at baseline ($P < 0.001$). The perioperative Hamilton Anxiety Scale and Hamilton Depression Scale scores of patients undergoing gynecological surgery decreased from (15.03 ± 3.16) and (13.93 ± 2.64) to (4.30 ± 1.15) and (3.53 ± 0.78), respectively, with statistically significant differences ($P < 0.001$). The perioperative Montreal Cognitive Assessment Scale score of the gynecological surgery patients increased from (23.17 ± 1.68) to (26.93 ± 1.11), also with statistical significance.

Research conclusions

MDT-based EBP of PH prevention and management in gynecological patients during the perioperative period can standardize nursing operations, improve nurses' awareness and behavioral compliance with gynecological hypothermia management, and reduce the occurrence of PH in gynecological patients, while playing a positive role in reducing patients' negative emotions and enhancing their cognitive function.

Research perspectives

MDT-based EBP has certain effectiveness in perioperative PH prevention and management of gynecological patients and can improve patients' psychological state and cognitive function. However, it is still necessary to solve the problem that the accuracy rate of intraoperative temperature monitoring is less than 80%.

FOOTNOTES

Author contributions: Liu QY designed the study; Liu QY, You TY, Zhang DY and Wang J performed the data collection and conducted the data analysis; Liu QY wrote the manuscript; Liu QY and Wang J revised the manuscript; all authors approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Effect of Internet + continuous midwifery service model on psychological mood and pregnancy outcomes for women with high-risk pregnancies

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Abstract

BACKGROUND

There are many drawbacks to the traditional midwifery service management model, which can no longer meet the needs of the new era. The Internet + continuous midwifery service management model extends maternal management from prenatal to postpartum, in-hospital to out-of-hospital, and offline to online, thereby improving maternal and infant outcomes. Applying the Internet + continuous midwifery service management model to manage women with high-risk pregnancies (HRP) can improve their psycho-emotional opinion and, in turn, minimize the risk of adverse maternal and/or fetal outcomes.

AIM

To explore the effectiveness of a midwife-led Internet + continuous midwifery service model for women with HRP.

METHODS

We retrospectively analyzed the clinical data of 439 women with HRP who underwent prenatal examination and delivered at Shanghai Sixth People's Hospital (affiliated to the Shanghai Jiao Tong University School of Medicine) from April to December 2022. Among them, 239 pregnant women underwent routine obstetric management, and 200 pregnant women underwent Internet + continuous midwifery service mode management. We used the State-Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale, and analysis of delivery outcomes to compare psychological mood and the incidence of adverse delivery outcomes between the two groups.

RESULTS

The data showed that in early pregnancy, the anxiety and depression levels of the two groups were similar; the levels gradually decreased as pregnancy progressed, and the decrease in the continuous group was more significant [31.00 (29.00, 34.00) *vs* 34.00 (32.00, 37.00), 8.00 (6.00, 9.00) *vs* 12.00 (10.00, 13.00), $P < 0.05$]. The maternal self-efficacy level and strategy for weight gain management were better in the continuous group than in the traditional group, and the effective rate of midwifery service intervention in the continuous group was significantly higher than in the control group [267.50 (242.25, 284.75) *vs* 256.00 (233.00, 278.00), 74.00 (69.00, 78.00) *vs* 71.00 (63.00, 78.00), $P < 0.05$]. The incidence of adverse delivery outcomes in pregnant women and newborns and fear of maternal childbirth were lower in the continuous group than in the traditional group, and nursing satisfaction was higher [10.50% *vs* 18.83%, 8.50% *vs* 15.90%, 24.00% *vs* 42.68%, 89.50% *vs* 76.15%, $P < 0.05$].

CONCLUSION

The Internet + continuous midwifery service model promotes innovation through integration and is of great significance for improving and promoting maternal and child health in HRP.

Key Words: Internet + continuous midwifery service; High-risk-pregnancy management; Psychological mood; Pregnancy outcome; Traditional midwifery service model; Midwife

Core Tip: The Internet + continuous midwifery service model promotes innovation through integration, breaks the limitations of time and space in the traditional midwifery service supply mode, and enables pregnant women to enjoy high-quality nursing services at home. However, it is necessary to determine the feasibility and effectiveness of the midwife-led Internet + continuous midwifery service model, especially in women with high-risk pregnancies (HRP). By retrospectively analyzing the clinical data of 439 women with HRP, we clarified the positive effect of the midwife-led Internet + continuous midwifery service model on the psychological mood and pregnancy outcomes of women with HRP.

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INTRODUCTION

High-risk pregnancies (HRP) are those with a high probability of dystocia, endangering the safety of the parturient and child. Data show that women with HRP in foreign countries account for 6% to 33% of all pregnant women[1], while the incidence of HRP in China is as high as 30%, which means that nearly one-third of pregnant women face adverse pregnancy outcomes such as dystocia, intrauterine death, postpartum hemorrhage, and puerperal infection. The National Institute for Health and Care Excellence (NICE) guidelines[2] indicate that effective communication, timely care, and treatment in early pregnancy, as well as professional care during and after delivery, can minimize the risk of adverse maternal and/or fetal outcomes.

In recent years, after a long period of practical exploration and theoretical research, domestic experts have achieved fruitful results in Internet + continuous midwifery service models. This service model overcomes the limitations of time and space of midwifery services, combines the advantages of the Internet, and gives full play to the subjective initiative of midwifery personnel. It can fully grasp the dynamic changes in parturients and newborns before, during, and after delivery and realize the long-term, continuous, and real-time management of pregnant and lying-in women by combining online and offline methods[3,4]. A systematic review pointed out that this nursing model enables pregnant women and midwives to establish partnerships during the prenatal, childbirth, and postpartum stages. Compared to other nursing models, it can reduce the necessity for maternal and infant treatment interventions[5]. Due to the gradual implementation of the Internet + continuous midwifery service model in maternal healthcare, a number of women with HRP were helped by the Internet + continuous midwifery service model between 2021 and 2022. However, it is necessary to determine the feasibility and effectiveness of the midwife-led Internet + continuous midwifery service model, especially the psychological emotions and pregnancy outcomes of women with HRP. This study retrospectively analyzed the role of the Internet + continuous midwifery service model for women with HRP.

MATERIALS AND METHODS

Patient characteristics

First, this was a retrospective study. Clinical data of 439 women with HRP, who underwent prenatal examination and delivered at Shanghai Sixth People's Hospital affiliated to the Shanghai Jiao Tong University School of Medicine from April 2022 to December 2022, were analyzed. According to the different midwifery service modes, participants were divided into a traditional group (TG, n = 239) and a continuous group (CG, n = 200). Inclusion criteria: (1) Age ≥ 18 years; (2) women with HRP with pregnancy risk assessment grade of "orange," "red," or "purple" in the "Maternal Pregnancy Risk Assessment and Management Standards" issued by the National Health and Family Planning Commission of the People's Republic of China; (3) women with HRP who can skillfully use an Internet smartphone; and (4) women with HRP who signed informed consent forms. Women with HRP with mental illness, who could not communicate, or lacked research data were excluded.

TG

The TG adopted a routine obstetric management mode; that is, the prenatal and postpartum stages were mainly managed by doctors, and midwives participated in the entire process of maternal production. During the prenatal checkup phase, obstetricians perform routine examinations and provide health education to pregnant women. In the waiting room, midwives provide prenatal care to pregnant women experiencing pain. In the delivery room, midwives assist parturients with delivery, perform lateral incisions, correctly assess fetal conditions, and provide basic care. An obstetric nurse is responsible for nursing management in the postpartum stage, such as health education, diet guidance, and puerperal care. On the day of discharge, the obstetric nurse provides health education to the parturient and instructs her to attend the obstetric clinic for review and health guidance 42 d after delivery.

CG

The CG implemented an Internet + continuous midwifery service model based on a traditional group, which was completed in three steps.

Step 1: Conduct expert meetings and establish a continuous midwifery service management team. Experts in related fields set up an expert group to put forward opinions and suggestions on the process and connotations of the Internet + continuous midwifery service mode. We have revised and improved these details. The continuous midwifery service management team comprised eight midwifery specialist nurses, three maternal and infant specialist nurses, and two neonatal specialist nurses. The head nurse of the department served as the group leader and was responsible for providing suggestions and opinions on the processes and connotations of continuous midwifery services. As the deputy leader, the head nurse was responsible for leading the team members to construct the initial implementation plan and organizing the members to carry out relevant training and assessment. In addition to participating in the above work, the remaining team members needed to implement Internet + continuous midwifery services for pregnant women.

Step 2: Establish an HRP Maternal Internet Communication Platform. During the recruitment of pregnant women participants, midwives invited them to join an Internet communication WeChat group and introduced WeChat group functions such as viewing popular science articles, downloading educational videos at different stages, and making group videos or voice calls. At the same time, team members were responsible for the implementation of WeChat group online interactions, irregularly and dynamically carrying out relevant health knowledge education for pregnant women and their families, and encouraging pregnant women to share their experiences and exchange experiences to indirectly alleviate maternal fear, anxiety, and other adverse psychological emotions. In addition, the midwives used videoconferencing software to regularly conduct pregnancy care courses and answer questions online. At the same time, the questionnaire star is used to collect relevant data.

Step 3: Carrying out Internet and continuous midwifery services. The midwife-led Internet + continuous midwifery service is divided into three periods: Prenatal stage [(1) first trimester < 14 wk; (2) 14-28 wk in the second trimester; and (3) > 28 wk in the third trimester), delivery stage (labor to 2 h after delivery), postpartum stage (4-6 wk after delivery)]. The specific process is shown in Figures 1 and 2.

Prenatal stages: Midwives used pregnancy anxiety, fear of childbirth, delivery efficiency, and weight management scales to evaluate the relevant situations of pregnant women. Based on the results of the nutritional analysis and the situation of the pregnant women, a personalized pregnancy management plan was initially formulated. The WeChat group regularly introduced knowledge related to pregnancy care, childbirth, and child-rearing every week through video teaching, text, pictures, and small videos. At this stage, midwives regularly used online video conference calls to communicate with pregnant women one-on-one to understand their needs and conditions. In the third trimester of pregnancy, midwives provided maternal health education related to the delivery stage, including delivery methods, processes, and techniques, and played introductory online videos of maternity wards and delivery rooms to familiarize them with the environment and relieve anxiety.

Delivery stage: During the period from labor to two hours after delivery of the placenta, the team leader selected team members to be responsible for midwifery according to the individual situation of the parturient and provided corresponding nursing services. This included the assessment of maternal and infant conditions, regular monitoring of maternal and fetal conditions, all basic care during labor and delivery, preliminary examination of newborns after delivery, breastfeeding, treatment of the placenta, perineal incision or wound suture, and registration of neonatal birth.

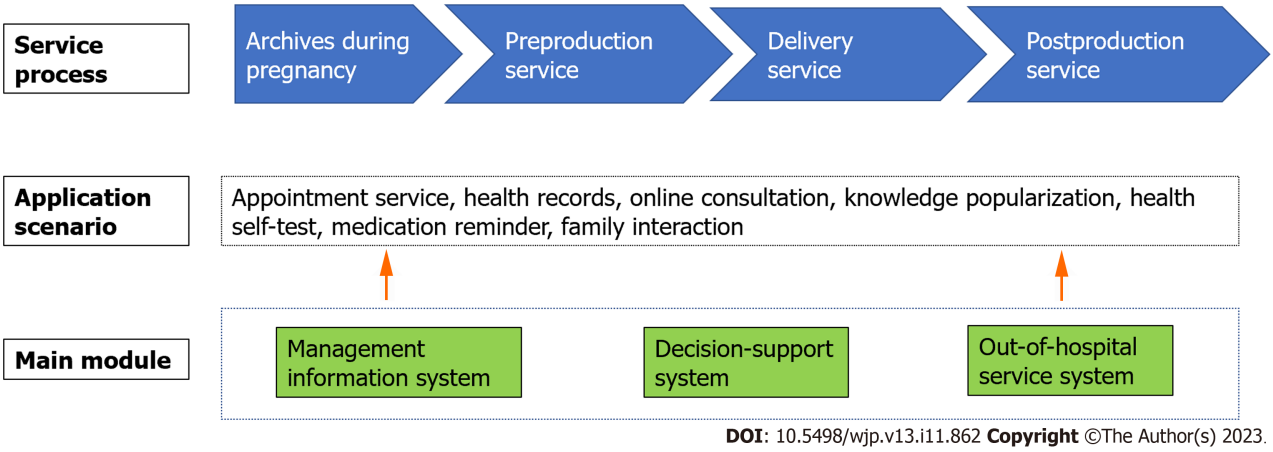

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Figure 1 Application of Internet in continuous midwifery service mode.

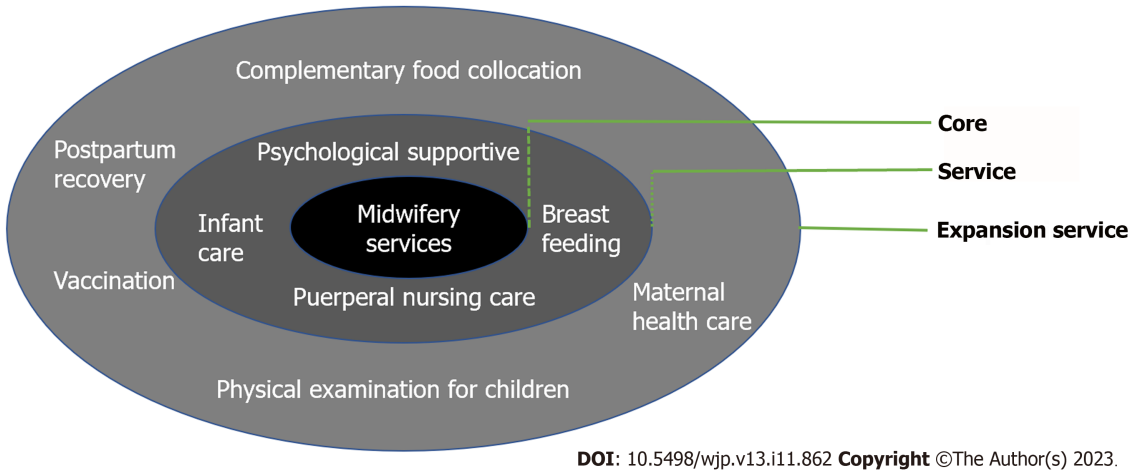

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Figure 2 Extension of out-of-hospital midwifery services.

Postpartum stage: Midwives provided postpartum health education for parturients and their families, including wound treatment, postpartum exercise nursing, neonatal feeding knowledge, and nursing. Midwives regularly communicated with parturients on WeChat every week to provide advice on puerperal care, breastfeeding, and maternal and child nutrition.

Effect evaluation

Main outcome measures: (1) Psychological Mood. The State-Trait Anxiety Inventory (STAI)[6] was used to evaluate anxiety. It included a total of 20 items, with a score of 1-4 and a total score of 20-80 points. The higher the score, the more serious the anxiety. The Edinburgh Postnatal Depression Scale (EPDS)[7,8] was used for the psychological assessment of depression, with a total of 10 items, a score of 0-3, and a total score of 0-30. Higher scores indicate more severe depression; and (2) Adverse delivery outcomes. The delivery outcomes of pregnant women and newborns were recorded, including postpartum hemorrhage, postpartum infection, premature rupture of membranes, neonatal asphyxia, fetal distress, fetal weight abnormalities, and premature delivery.

Secondary outcome: (1) Self-efficacy. A simplified Chinese version of the Childbirth Self-Efficacy Scale (CBSEI-C32)[9] was used for the measurements. The total score ranges from 32 to 320 points. Higher scores indicate higher delivery self-efficacy; (2) Childbirth Attitudes Questionnaire (CAQ)[10] was used to assess the fear of childbirth for women in late pregnancy. The total score was 16-64 points, with < 28 points indicating no fear of childbirth, 28-39 points indicating mild fear, 40-51 points indicating moderate fear, and 52-64 points indicating high fear; (3) Weight management. Pregnancy Weight Management Strategy Scale (PWMSS)[11] consists of 18 items, a 1-5 grade score, and a total score of 18-90 points. The higher the score, the more weight gain management strategies were used during pregnancy; and (4) Maternal nursing satisfaction was assessed using a self-administered nursing satisfaction questionnaire.

Statistical analysis

All data were analyzed using SPSS 24.0. Enumeration data were expressed as frequencies and constituent ratios, and

Table 1 Clinical information of women with high-risk pregnancies

Variables	TG (*n* = 239)	CG (*n* = 200)	χ^2/*Z* value	*P* value
Age (yr), IQR	29.00 (27.00, 32.00)	30.00 (26.25, 33.00)	-1.591	0.112
Types of pregnant women, *n* (%)			2.196	0.138
Primipara	49 (20.50)	53 (26.50)		
Pluripara	190 (79.50)	147 (73.50)		
Educational level, *n* (%)			0.415	0.813
Junior high school and below	40 (16.70)	37 (18.50)		
High school or technical secondary school	124 (51.80)	98 (49.00)		
Junior college and above	75 (31.30)	65 (32.50)		
HRP factor, *n* (%)				
Pregnancy complication	87 (36.40)	68 (34.00)	0.275	0.600
Abnormal body mass index	54 (22.50)	33 (16.50)	2.545	0.111
Scarred uterus	41 (17.10)	37 (18.50)	0.135	0.713
Adverse pregnancy	40 (16.70)	31 (15.50)	0.123	0.726
Arrhythmia	39 (16.30)	25 (12.50)	1.275	0.259

Pregnancy complications refer to pregnancy with anemia, diabetes, hypertension, *etc*.; Abnormal body mass index (BMI) refers to a BMI > 25 kg/m^2 or < 18.5 kg/m^2; The same women with high-risk pregnancies can experience two or more risk factors. HRP: High-risk pregnancies; IQR: Interquartile range; TG: Traditional group; CG: Continuous group.

measurement data with a non-normal distribution were expressed as interquartile ranges. Enumeration data were analyzed by χ^2 test, and measurement data were analyzed by a nonparametric Mann-Whitney *U* test. Repeated-measures analysis of variance was used to analyze the results of multiple measurements. The rank-sum test was used for the grade data. $P < 0.05$ was considered as statistically significant.

RESULTS

Clinical characteristics

There was no statistical difference in the general clinical data between the two groups ($P > 0.05$) (Table 1).

Psychological and emotional changes in women with HRP

In the first trimester, the anxiety and depression levels of the two groups were similar and decreased gradually as pregnancy progressed; the CG decreased more significantly ($P < 0.05$) (Table 2).

Self-efficacy changes of women with HRP

There was no statistically significant difference between the two groups in the CBSEI-C32 scores in the first trimester ($P > 0.05$). The CBSEI-C32 scores increased as pregnancy progressed ($P < 0.05$), and the extent of the increase in the CG was greater than that in the TG ($P < 0.05$) (Table 3).

The fear of childbirth in women with HRP in the third trimester of pregnancy

Overall, the effectiveness rate of midwifery interventions in the CG was significantly higher than that in the TG, and the degree of maternal fear of childbirth was lower; the difference was statistically significant ($Z = -4.190$, $P < 0.05$) (Figure 3).

Weight management during pregnancy for women with HRP

In early pregnancy, there was no significant difference in PWMSS scores between the two groups ($P > 0.05$). The PWMSS score increased with an increase of pregnancy ($P < 0.05$). The PWMSS scores of the CG were better than those of the TG ($P < 0.05$) (Table 4).

Adverse birth outcome

In the TG, the incidence of adverse birth outcomes was 18.83% (45/239), and the incidence of adverse neonatal outcomes was 15.90% (38/239). In the CG, the incidence of adverse birth outcomes was 10.50% (21/200), and the incidence of adverse neonatal outcomes was 8.50% (17/200). The CG level was lower than the TG level (all $P < 0.05$) (Table 5).

Table 2 Psychological and emotional changes of women with high-risk pregnancies

Groups		First trimester	Second trimester	Late pregnancy	Postpartum	*F* value	*P* value
Anxiety	TG	65.00 (60.00, 70.00)	57.00 (53.00, 61.00)	40.00 (37.00, 43.00)	34.00 (32.00, 37.00)	215.238	< 0.05
	CG	64.50 (59.00, 68.00)	50.00 (46.00, 54.00)	36.00 (31.25, 40.00)	31.00 (29.00, 34.00)		
	Z value	-1.095	-10.591	-7.703	-7.913		
	P value	0.274	< 0.05	< 0.05	< 0.05		
Depression	TG	22.00 (20.00, 24.00)	19.00 (17.00, 22.00)	19.00 (16.00, 21.00)	12.00 (10.00, 13.00)	196.103	< 0.05
	CG	22.00 (19.00, 24.00)	17.00 (14.25, 19.00)	15.00 (13.00, 17.00)	8.00 (6.00, 9.00)		
	Z value	-0.530	-5.941	-11.048	-12.116		
	P value	0.596	< 0.05	< 0.05	< 0.05		

TG: Traditional group; CG: Continuous group.

Table 3 Changes of self-efficacy in women with high-risk pregnancies

Groups	First trimester	Second trimester	Late pregnancy	Postpartum	*F* value	*P* value
TG	90.00 (83.00, 96.00)	133.00 (123.00, 148.00)	202.00 (187.00, 223.00)	256.00 (233.00, 278.00)	462.402	< 0.05
CG	92.00 (82.00, 97.00)	152.00 (139.00, 165.00)	234.50 (214.25, 257.75)	267.50 (242.25, 284.75)		
Z value	-0.802	-8.374	-9.794	-3.229		
P value	0.423	< 0.05	< 0.05	0.001		

TG: Traditional group; CG: Continuous group.

Table 4 Changes in weight management in women with high-risk pregnancies

Groups	First trimester	Second trimester	Late pregnancy	Postpartum	*F* value	*P* value
TG	33.00 (29.00, 38.00)	42.00 (37.00, 47.00)	68.00 (60.00, 73.00)	71.00 (63.00, 78.00)	30.284	< 0.05
CG	33.00 (28.00, 36.00)	45.00 (40.00, 50.00)	68.00 (64.00, 73.00)	74.00 (69.00, 78.00)		
Z value	-0.743	-3.992	-2.004	-3.059		
P value	0.458	< 0.05	0.045	0.002		

TG: Traditional group; CG: Continuous group.

Table 5 Adverse pregnancy outcomes of parturients and child, *n* (%)

Groups	Parturients				X^2 value	*P* value	Child				X^2 value	*P* value
	Postpartum hemorrhage	Postpartum infection	Premature rupture of membranes	Other			Neonatal asphyxia	Premature delivery	Abnormal fetal weight	Other		
TG	15 (6.28)	9 (3.77)	8 (3.35)	13 (5.44)	5.912	0.015	8 (3.35)	11 (4.60)	7 (2.93)	12 (5.02)	5.44	0.02
CG	7 (3.50)	4 (2.00)	3 (1.50)	7 (3.50)			3 (1.50)	5 (2.50)	2 (1.00)	7 (3.50)		

TG: Traditional group; CG: Continuous group.

Table 6 Nursing satisfaction

Groups	Not satisfied	More satisfactory	Satisfaction	Great satisfaction
TG	59	61	49	70
CG	21	31	55	93
Z value	-5.050			
P value	< 0.05			

TG: Traditional group; CG: Continuous group.

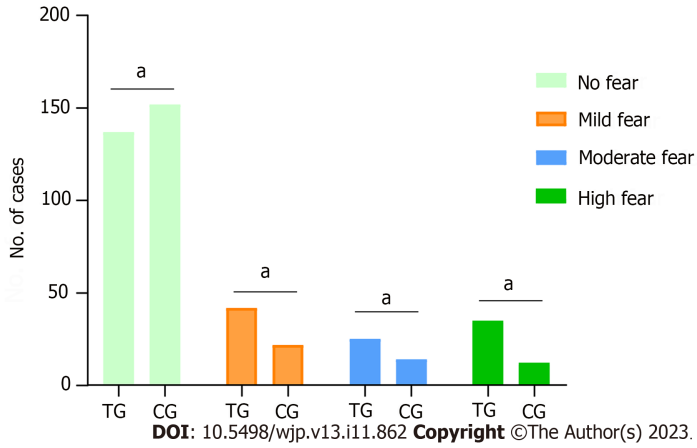

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Figure 3 Fear of childbirth in late pregnancy of two groups of pregnant women. [a]P < 0.05. TG: Traditional group; CG: Continuous group.

Nursing satisfaction

In the CG, nursing satisfaction was 89.50%, which was significantly higher than 76.15% in the TG ($P < 0.05$) (Table 6).

DISCUSSION

The World Health Organization has reported that 50% of maternal deaths and more than 60% of neonatal deaths are caused by poor quality of care. Midwives who have received international standard education can provide women with planned pregnancy guidance and 87% of parturients and child basic care needs, while also avoiding more than 80% of maternal deaths, stillbirths, and neonatal deaths[12]. Among these, the quality of nursing before and after delivery and during puerperium is the focus of promoting maternal health. Prenatal monitoring and postpartum rehabilitation nursing are difficult to perform. It is difficult to fully understand the situation of parturients and newborns by simply relying on community home visits. To meet the nursing needs of women with HRP and compensate for the shortcomings of traditional maternal care services, the Internet + continuous midwifery service model, led by hospital midwives and combined with the advantages of the Internet, provides care to women with HRP and improves adverse pregnancy outcomes.

Regarding the prevalence of anxiety and depression in women with HRP, Dagklis *et al*[13,14] studied the incidence of depression in two HRP inpatient maternal samples (24.3% and 28%, respectively). Goetz *et al*[15] reported significant results. We found a similar trend in this study when compared to recently published inpatient samples. Women with HRP had significantly higher levels of anxiety and depression during early pregnancy. After the intervention of the Internet + continuous midwifery services, the levels of anxiety and depression gradually decreased as pregnancy progressed. As far as we know, the anxiety and depression of women with HRP are caused by many factors. On the one hand, the fear, worry, and pressure of coronavirus disease 2019 may endanger their own and fetal life and health; on the other hand, women with HRP are constrained by time and transportation problems and are unable to perform pregnancy tests on time, thus creating anxiety[16]. From the perspective of the space in which pregnant women receive midwifery services, traditional midwifery services are limited to the management process of pregnant women in hospital, unable to effectively supervise and guide pregnant women outside hospital and predict in advance the risk signals that may trigger HRP or produce adverse pregnancy outcomes. In the Internet + continuous midwifery service dominated by midwives, relying on the WeChat communication group, midwives can provide long-term, continuous, and real-time health counseling for pregnant women, management of normal pregnancy, delivery and puerperium, neonatal care, follow-up postpartum rehabilitation, women's health care, children's physical examinations, and vaccinations[17,18]. In long-term communication, midwives and pregnant women form a stable nurse-patient relationship, reduce the psychological

burden on pregnant women, and alleviate anxiety and depression[19]. Self-efficacy refers to the belief that an individual can perform certain behavioral operations. It plays an important role in controlling or adjusting individual behavior and is related to psychological emotions[20]. Studies have found that the main cause of maternal anxiety is uncertainty in the delivery process and that good self-efficacy can reduce anxiety[21]. The above shows that Internet + continuous midwifery services can effectively improve the psychological mood of women with HRP and improve their self-efficacy.

The self-management ability of pregnant women plays an indispensable role in weight control during pregnancy, especially in compliance and daily life behaviors of pregnant women. Internet + continuous midwifery service completes the monitoring of health indicators independently by adopting online and offline methods, enhancing the sense of self-control of perinatal health care, promoting the formation of good self-management consciousness in pregnant women, and promoting the transformation of health behavior[22]. Ge *et al*[11] found that the self-efficacy of pregnant women can affect their weight management behaviors. Pregnant women can have a high degree of self-evaluation after realizing that they can manage their pregnancy weight well, which promotes weight management behaviors.

Due to the separate nature of previous midwifery services, contact between midwives and pregnant women was limited by time and space, resulting in problems such as a lack of knowledge and fear of childbirth. In CG, mobile Internet technology can effectively meet the diverse needs of pregnant women during pregnancy[23]. Midwives encouraged their families to participate in the learning of knowledge during pregnancy, delivery, and postpartum, and understand the psychological and physiological changes of pregnant women. They can provide pregnant women with more emotional support and positive encouragement during labor, which is conducive to reducing the fear of childbirth and achieving good pregnancy outcomes. This is consistent with the results of a previous study[5]. In addition, midwives work closely with the grassroots medical staff to cooperate and support each other in providing extended midwifery services. When necessary, midwives can use Internet technology to achieve information sharing and two-way referrals.

CONCLUSION

The combination of Internet- and midwife-led continuous midwifery services can effectively expand the use of high-quality nursing service resources, realize the integrated management of women with HRP before and after delivery, and support special groups of women with HRP. Midwives provide effective, economical, and convenient personalized nursing measures for pregnant women during pregnancy, childbirth, and puerperium, which not only reduces the anxiety and depression of women with HRP, but also improves the quality of life of women with HRP and newborns.

ARTICLE HIGHLIGHTS

Research background

There are many drawbacks to the traditional midwifery service management model that can no longer meet the needs of the new era. Dominated by midwives and combined with the advantages of the Internet, continuous midwifery services are provided to women with high-risk pregnancies (HRP) to alleviate adverse psychological emotions and improve pregnancy outcomes.

Research motivation

It is necessary to determine the feasibility and effectiveness of the midwife-led Internet + continuous midwifery service model, especially the psychological emotions and pregnancy outcomes of women with HRP.

Research objectives

To analyze the effect of a midwife-led Internet + continuous midwifery service model on the psychological mood and pregnancy outcomes of women with HRP.

Research methods

The clinical data of 439 women with HRP were retrospectively analyzed. They were divided into different midwifery service modes (traditional and continuous groups). Psychological and emotional conditions, self-efficacy, incidence of adverse delivery outcomes, and nursing satisfaction were compared between the two groups.

Research results

The State-Trait Anxiety Inventory and Edinburgh Postnatal Depression Scale scores of the two groups gradually decreased, with the continuous group decreasing faster than the traditional group. The incidence of adverse delivery and neonatal outcomes in the continuous group was 10.50% (21/200) and 8.50% (17/200), respectively, significantly lower than in the traditional group (18.83%, 45/239; 15.90%, 38/239, respectively).

Research conclusions

The Internet + continuous midwifery service model gives full play to the subjective initiatives of pregnant women and midwives. It is of great significance to realize long-term, continuous, and real-time maternal management and ensure maternal and child safety through "prenatal-intrapartum-postpartum," in-hospital and out-of-hospital, online, and offline

care.

Research perspectives

Midwives carry out corresponding Internet services according to different stages of pregnancy (early, middle, and late pregnancy), including the release of popular science articles on the public account, WeChat group communication, questionnaire star collection of relevant information, and network video conferences answering questions to guide women with HRP to carry out prenatal examinations and self-monitoring. Midwives can not only provide professional advice during pregnancy and childbirth but also provide extended quality nursing services to improve maternal satisfaction.

FOOTNOTES

Author contributions: Han W and Huang CJ contributed to the conceptualization; Han W contributed to the methodology; Huang CJ contributed to the writing; Huang CQ contributed to the data curation and formal analysis.

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Informed consent statement: As this is a retrospective study, an exemption from informed consent has been applied for.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the relationship between blood pressure variability and subtle cognitive decline in older adults

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Abstract

BACKGROUND

Blood pressure variability (BPV) has been shown to be related to mild cognitive impairment and Alzheimer's disease in a number of studies. However, the relationship between BPV and subtle cognitive decline (SCD) has received minimal attention in this field of research to date and has rarely been reported.

AIM

To examine whether SCD is independently associated with changes in BPV in older adults.

METHODS

Participants were selected based on having participated in cognitive function evaluation and ambulatory blood pressure measurement at the Shanghai Sixth People's Hospital Affiliated with Shanghai Jiao Tong University School of Medicine between June 2020 and August 2022. The participants included 182 individuals with SCD as the experimental group and 237 with normal cognitive function as the control group. The basic data, laboratory examinations, scale tests, and ambulatory blood pressure test results of the two groups were analyzed retrospectively, and the relationship between SCD and BPV was subsequently evaluated.

RESULTS

Significant differences were observed between the two groups of participants ($P < 0.05$) in terms of age, education level, prevalence rate of diabetes, fasting blood glucose level, 24-h systolic blood pressure standard deviation and coefficient of

variation, 24-h diastolic blood pressure standard deviation and coefficient of variation. The scale monitoring results showed significant differences in the scores for memory, attention, and visual space between the experimental and control groups. Logistic regression analysis indicated that age, education level, blood sugar level, and BPV were factors influencing cognitive decline. Linear regression analysis showed that there was an independent correlation between blood pressure variation and SCD, even after adjusting for related factors. Each of the above differences was still significant.

CONCLUSION
This study suggests that increased BPV is associated with SCD.

Key Words: Blood pressure; Variability; Elderly; Subtle cognitive decline relationship

Core Tip: Cognitive dysfunction is a disease that seriously endangers human health, and its current treatment measures are far from perfect. Early identification, which can facilitate the implementation of early treatment, is the primary focus of this research. Our aim was to explore the correlation between blood pressure variability (BPV) and subtle cognitive decline and to understand whether BPV can be used for early detection of cognitive impairment.

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INTRODUCTION

Alzheimer's disease (AD) is a highly harmful disease. Epidemiological surveys have shown that there are more than 30 million AD patients globally, and it is expected that in 30 years, this number will have expanded to 130 million. Cognitive impairment resulting from AD is serious and irreversible, carries a high disability rate, and is difficult to cure, placing a huge burden on both families and society as a whole[1,2]. Although much work has already been performed in this area, there remains no truly effective therapy for AD. Early identification, screening, detection, and intervention are important for preventing the progression of the disease[3-6]. The National Institute on Aging and the Alzheimer's Association have classified AD into three distinct stages[7]: The AD preclinical stage [subjective cognitive decline and subtle cognitive decline (SCD), AD-derived mild cognitive impairment (MCI), and the dementia stage]. SCD refers to the initial phase of cognitive decline. Memory loss is the primary symptom of AD during this period, although a routine examination cannot indicate MCI caused by dementia. According to prior research, early identification and prompt intervention can help prevent 30% of the risk factors associated with AD[4,8,9]. Therefore, SCD has become a popular topic in early-stage AD research. Unlike gene testing, cerebrospinal fluid, and positron emission tomography (PET), blood pressure variability (BPV) testing is inexpensive, non-invasive, and easy for patients to accept. Determining the correlation between BPV and cognitive impairment can provide valuable insight for clinicians regarding the process of diagnosis and treatment.

BPV, also known as blood pressure volatility, indicates the degree to which an individual's blood pressure fluctuates during a certain period of time and does not depend on blood pressure levels[10-12]. BPV is an indicator of spontaneous fluctuations in blood pressure, which are closely related to arterial remodeling, left ventricular hypertrophy, stroke, and hypertensive renal damage. In the physiological process that emerges during the progression from hypertension to cardio-cerebrovascular events, BPV plays an adverse role at every stage[13-16]. Blood pressure changes that occur within 24 h (short-term BPV) are more valuable for predicting the risk of cardiovascular death than clinical blood pressure. Previously published articles have found that the predictive effect of clinical blood pressure is limited, and short-term BPV can serve as a more accurate indicator than clinical blood pressure; therefore, the use of ambulatory blood pressure monitoring (ABPM) should be widely promoted over the use of clinical blood pressure[17-19]. Previous studies have shown that that BPV is associated with MCI and AD[20-22], but studies on BPV and SCD to date have proven rare. SCD is an early stage of AD, and those with SCD face a significantly higher risk of developing MCI and AD people with SCD than those with normal cognitive function[23-25]. Our aim was to evaluate the correlation between BPV and SCD and to analyze whether BPV could be used as a screening index for early cognitive decline.

MATERIALS AND METHODS

Participants

From June 2020 to August 2022, 1095 people who participated in a routine physical examination at the Department of

Geriatrics of Shanghai Sixth People's Hospital completed the neuropsychological scale test and 24-h ABPM. According to the test results, 237 individuals had normal cognitive function and were classified as the control group (NC), and 182 had SCD and were classified as the experimental group (SCD). The basic data, laboratory examinations, scale tests, and ABPM test results of the SCD and NC groups were retrospectively analyzed, and the relationship between BPV and SCD was subsequently assessed.

Inclusion criteria: (1) Participants aged 60 or older; (2) those who have a primary school level education or higher; and (3) those who possess a normal level of hearing and eyesight.

Exclusion criteria: (1) Patients with MCI and AD; (2) those with a history of cerebrovascular disease, such as brain trauma, cerebral infarction, cerebral hemorrhage, Parkinson's disease, brain tumor, epileptic psychosis, or dysplasia; (3) those with a Hamilton Depression Rating Scale 17-item score of more than 12; (4) those with other diseases affecting cognitive function, such as B12 deficiency, alcoholism, folic acid, drug abuse, syphilis, and AIDS; (5) those with visual impairment, hearing impairment, and limb dysfunction resulting in an inability to complete the neuropsychological scale; and (6) those with serious diseases in major organs, such as the liver, kidneys, heart, and lungs.

Clinical-demographic data

Participants' sex, age, height, weight, educational attainment, and history of chronic diseases were recorded. On the same day, routine blood tests, blood lipids, liver and kidney function, and blood glucose were checked, and a head magnetic resonance imaging examination was conducted.

Cognitive function

In a specialized neuropsychological room, the scale was assessed by trained professionals. Scale detection participants did not participate in the judgment of cognitive diagnosis. Each participant was screened using strict scale tests to assess memory, space, attention, language, execution, and social cognition; the scales utilized included a mini-mental state examination (MMSE), the Chinese version of the Montreal Cognitive Assessment (MoCA; MoCA-CV), Hamilton Depression Scale, Auditory Verbal Learning Test (AVLT), Animal Verbal Fluency Test (AFT), Boston Naming Test (BNT), Symbol Digit Modalities Test (SDMT), Rey-Osterrieth Complex Figure Test (CFT), Trail Making Test Part A (TMT-A) and part B (TMT-B), Prospective Memory Test (PrM), Functional Activities Questionnaire (FAQ), and so on.

ABPM and BPV indices

Twenty-four-hour ABPM: The testing period was from 7:00 on day one to 7:00 the following day, from 7:00 to 21:59 during the day, and was recorded every 30 minutes. At nighttime, the testing period was from 22:00 to 6:59 on the second day, with tests taken every 60 min. To be included in the group, the valid readings had to be greater than 90%. BPV indices included 24-h systolic blood pressure standard deviation (SBP SD) and coefficient of variation (SBP CV) as well as 24-h diastolic blood pressure standard deviation (DBP SD) and coefficient of variation (DBP CV). The coefficient of variation was calculated using the formula CV = 100 × SD/mean.

Biochemical indicators

On the day of the scale test, after fasting for 8 h, venous blood samples were taken and immediately tested for blood glucose (fasting and two hours postprandial blood glucose), blood lipids, serum creatinine, serum uric acid, and so on.

Diagnostic criteria of SCD

A total of six neuropsychological scores were examined using the method by Jak and Bondi: the AFT and a 30-item BNT were administered to evaluate language; the TMT-A and TMT-B were administered to evaluate attention/executive function; and two scales were applied to evaluate memory function - the Rey AVLT, a 30-min delayed free recall test, and AVLT recognition. The criteria were used to determine whether participants had SCD: (1) Cognitive decline on two of the six neuropsychological measures in different cognitive fields, defined as > 1 SD below the age-corrected normative mean; and (2) a FAQ score of 6-8[23].

Statistical analysis

The statistical analysis was conducted using SPSS 24.0. We used the mean ± SD to represent the measurement data, and a *t*-test was applied to compare the NC and SCD groups. A χ^2 test was utilized to compare the counting data between the two groups. A binary logistic regression was used to analyze the related factors of cognitive impairment, and a multiple linear regression was performed to determine cognitive domain scores were correlated with BPV. The level of significance was set at $P \leq 0.05$.

RESULTS

Demographic characteristics of the subjects

Table 1 presents the general characteristics of the participating researchers. Significant differences were observed in age, education level, incidence of diabetes, fasting blood glucose levels, SBP SD, SBP CV, DBP SD, and DBP CV between the NC ang SCD groups. No significant differences in other indices were observed.

Table 1 General characteristics of participants

	NC (*n* = 237)	SCD (*n* = 182)	*P* value
Age, yr	70.35 ± 9.57	72.19 ± 10.31	0.002
Sex (male, %)	169 (71.31%)	127 (69.78%)	0.219
Education, yr	11.49 ± 4.12	10.05 ± 3.79	0.037
BMI (kg/m^2)	22.47 ± 4.91	23.16 ± 5.03	0.291
Smoking, *n* (%)	51 (21.52)	39 (21.43)	0.479
Drinking, *n* (%)	72 (30.38)	57 (31.32)	0.517
Hypertension, *n* (%)	104 (43.88)	83 (45.60)	0.153
Diabetes, *n* (%)	35 (14.77)	31 (17.03)	0.021
CAD, *n* (%)	29 (12.24)	27 (14.84)	0.149
FBG (mmol/L)	5.41 ± 1.17	5.93 ± 1.61	0.037
PBG (mmol/L)	8.75 ± 2.81	8.59 ± 2.63	0.275
Scr (μmol/L)	82.45 ± 29.51	79.43 ± 28.72	0.117
TC (mmol/L)	4.53 ± 1.37	4.19 ± 0.95	0.093
TG (mmol/L)	1.32 ± 0.75	1.42 ± 0.81	0.055
HDL-C (mmol/L)	1.15 ± 0.51	1.17 ± 0.49	0.213
LDL-C (mmol/L)	2.39 ± 0.83	2.21 ± 0.79	0.314
SBP SD	10.52 ± 2.94	14.15 ± 4.37	0.000
DBP SD	7.32 ± 2.74	9.45 ± 3.07	0.040
SBP CV	12.35 ± 3.74	16.97 ± 4.91	0.000
DBP CV	9.85 ± 2.73	12.63 ± 3.81	0.006

NC: The control group; SCD: Subtle cognitive decline; BMI: Body mass index; CAD: Coronary artery disease; FBG: Fasting blood glucose; PBG: Postprandial blood glucose; Scr: Serum creatinine; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; SBP SD: 24-h systolic blood pressure standard deviation; SBP CV: 24-h systolic blood pressure coefficient of variation; DBP SD: 24-h diastolic blood pressure standard deviation; DBP CV: 24-h diastolic blood pressure variation coefficient.

Cognitive scale score

As shown in Table 2, a significant difference was observed between the two groups on the MMSE and the MoCA. A comparison of the scores for each cognitive domain revealed significant differences in attention, memory, and visual space between the two groups.

Analysis of influencing factors of cognitive impairment

Using cognitive decline as a dependent variable and other influencing factors as independent variables, multivariate logistic regression analysis revealed that cognitive decline was significantly correlated with age, education level, diabetes, SBP SD, DBP SD, SBP CV, and DBP CV (Table 3).

Effect of blood pressure variation on cognitive performance

Multiple linear regression analysis demonstrated that memory, attention, and visual-spatial dysfunction in the SCD group were significantly correlated with SBP SD and CV, while DBP SD and CV were significantly correlated with memory impairment. Even adjusting for age, sex, drinking, smoking, education level, body mass index, blood glucose, and blood lipid levels, these differences remained significant (Table 4).

DISCUSSION

This study aimed to identify a simple method for detecting cognitive decline in its early stages. In this retrospective study, BPV was observed to be independently associated with SCD and increased BPV in individuals aged 60 or above and may be seen as a risk factor for SCD.

Current reports on the correlation between BPV and cognitive impairment are inconsistent. Most researchers believe that cognitive impairment is associated with increased BPV. However, different views have been expressed on this topic,

Table 2 Scores of personnel cognition scale in two groups

Index	NC (*n* = 207)	SCD (*n* = 175)	*F* (*P* value)
MMSE	28.97 ± 2.13	26.15 ± 1.62	49.327 (< 0.001)
MoCA	25.74 ± 2.96	22.93 ± 3.27	57.319 (< 0.001)
AVLT recognition	21.39 ± 5.27	19.31 ± 3.77	3.572 (0.041)
AVLT delayed recall	6.32 ± 2.29	4.17 ± 1.59	8.351 (0.011)
BNT	24.15 ± 3.14	22.59 ± 3.57	0.275 (0.179)
SDMT	39.29 ± 12.57	34.26 ± 11.09	4.529 (0.032)
TMT-A	53.14 ± 23.95	57. 83 ± 26.71	0.127 (0.359)
TMT-B	133.49 ± 39.72	154.97 ± 45.21	5.273 (0.019)
Rey CFT copy	34.59 ± 3.71	31.49 ± 4.25	8.319 (0.014)
Rey CFT recall	16.72 ± 5.93	13.27 ± 6.41	9.592 (< 0.001)
AFT	16.79 ± 4.52	16.32 ± 4.17	0.035 (2.531)
PrM	14.31 ± 4.15	12.29 ± 4.52	3.572 (0.031)

NC: The control group; SCD: Subtle cognitive decline; MMSE: Mini-mental State Examination; MoCA: Montreal Cognitive Assessment; AVLT: Auditory Verbal Learning Test; BNT: Boston Naming Test; SDMT: Symbol Digit Modalities Test; TMTA, TMT-B: Trail Making Test Part A and B; Rey CFT: Rey-Osterrieth Complex Figure Text; AFT: Animal Fluency Test; PrM: Prospective Memory Test.

Table 3 Logistic regression analysis influencing factors of cognitive impairment

Index	β	SE	Wald	*P* value	OR	95%CI
Age	0.37	0.09	17.59	0.000	1.63	1.45-1.81
Education	0.75	0.13	20.31	0.000	1.92	1.75-2.31
Diabetes	0.11	0.03	13.27	0.000	1.21	1.09-1.37
SBP SD	1.31	0.24	26.15	0.000	3.95	2.57-4.72
SBP CV	0.95	0.21	30.63	0.000	3.71	2.69-4.63
DBP SD	2.47	0.61	8.59	0.023	9.72	3.51-18.95
DBP CV	0.85	0.19	27.33	0.002	3.01	2.65-3.91

SBP SD: 24-h systolic blood pressure standard deviation; SBP CV: 24-h systolic blood pressure coefficient of variation; DBP SD: 24-h diastolic blood pressure standard deviation; DBP CV: 24-h diastolic blood pressure coefficient of variation.

such as that higher BPV has nothing to do with dementia[26-28]; that patients with increased BPV have higher cognitive scores; and that only the increase in systolic blood pressure variation is related to cognitive decline, while the increase in diastolic blood pressure variation is not. In addition, there are significant differences in the cognitive assessment tools, BPV calculation method, duration of blood pressure monitoring, study population, and sample size among different studies[29-31]. Thus, standardized methods should be considered to compare and determine the significance of various studies. The results of the 24-h ABPM were used to calculate BPV, which is a more objective form of measurement than clinic blood pressure; the equipment is simple, primary medical institutions can use it, and research participants can easily accept this method.

At present, effective treatment for dementia remains far from perfect, and many people with cognitive impairment seek treatment in community medical institutions. Identifying changeable risk factors is important for preventing dementia in primary healthcare institutions. ABPM to evaluate blood pressure levels and BPV is a simple method for assessing the risk of dementia and evaluating the effectiveness of treatment.

There are several viewpoints on the mechanism underlying cognitive impairment caused by BPV[32-36]: (1) Hemodynamic instability has harmful effects on neurovascular units and results in endothelial injury and vascular smooth muscle dysfunction, leading to accelerated neuronal damage and neuronal loss; (2) arterial remodeling is beneficial to β-amyloid deposition and reactive glial hyperplasia; (3) the fluctuation of arterial blood pressure leads to inconsistent perfusion attacks of tissue hypoxia-ischemia, promoting the activation of microglia and the production of brain amyloid proteins, resulting in neuronal injury and cell death; and (4) oxidative stress and inflammation. There may be direct connections between vascular and metabolic factors and the deposition of β-amyloid proteins in the brain,

Table 4 Correlation between blood pressure variability and cognitive function by multivariate linear regression analysis

Outcome		Unadjusted model	*P* value	Adjusted model 1	*P* value	Adjusted model 2	*P* value
		β (95%CI)		β (95%CI)		β (95%CI)	
Memory	SBP SD	-0.82 (-1.17 to -0.49)	< 0.001	-0.57 (-0.91 to -0.22)	< 0.001	-0.51 (-0.89 to -0.21)	< 0.001
	SBP CV	-0.79 (-1.15 to -0.42)	< 0.001	-0.61 (-0.93 to -0.32)	< 0.001	-0.59 (-0.91 to -0.25)	< 0.001
	DPB SD	-0.31 (-0.56 to -0.07)	< 0.05	-0.29 (-0.51 to -0.08)	0.029	-0.27 (-0.49 to -0.07)	0.035
	DPB CV	-0.27 (-0.55 to 0.01)	0.037	-0.26 (-0.47 to -0.08)	0.041	-0.23 (-0.41 to -0.03)	0.049
Language	SBP SD	0.04 (-0.02 to 0.09)	0.155	0.03 (-0.01 to 0.07)	0.165	0.03 (-0.02 to 0.09)	0.172
	SBP CV	0.04 (-0.01 to 0.11)	0.153	0.03 (-0.01 to 0.09)	0.167	0.03 (-0.02 to -0.10)	0.157
	DPB SD	0.11 (-0.01 to 0.23)	0.241	0.09 (0.02 to 0.19)	0.305	0.09 (0.01 to 0.18)	0.291
	DPB CV	0.08 (-0.02 to 0.17)	0.195	0.07 (-0.01 to 0.15)	0.236	0.07 (-0.02 to 0.16)	0.229
Attention	SBP SD	-0.76 (-1.07 to -0.39)	< 0.001	-0.67 (-1.03 to -0.21)	< 0.001	-0.70 (-1.01 to -0.39)	< 0.001
	SBP CV	-0.69 (-0.95 to -0.27)	< 0.001	-0.61 (-0.93 to -0.25)	< 0.001	-0.59 (-0.87 to -0.31)	< 0.001
	DPB SD	-0.17 (-0.35 to 0.02)	0.09	-0.11 (-0.32 to 0.01)	0.13	-0.12 (-0.31 to 0.02)	0.13
	DPB CV	-0.15 (-0.29 to -0.01)	0.08	-0.09 (-0.03 to 0.02)	0.15	-0.08 (-0.02 to 0.03)	0.17
Visuospatial ability	SBP SD	-0.27 (-0.39 to -0.14)	< 0.01	-0.21 (-0.35 to -0.10)	< 0.01	-0.20 (-0.33 to 0.06)	< 0.01
	SBP CV	-0.31 (-0.42 to -0.21)	< 0.01	-0.27 (-0.39 to -0.14)	< 0.01	-0.22 (-0.40 to -0.05)	< 0.01
	DPB SD	-0.11 (-0.25 to -0.03)	0.147	-0.07 (-0.02 to 0.03)	0.163	-0.06 (-0.02 to 0.01)	0.179
	DPB CV	-0.15 (-0.29 to 0.01)	0.133	-0.08 (-0.19 to 0.02)	0.182	-0.08 (-0.18 to 0.03)	0.195
Executive function	SBP SD	0.16 (0.05 to 0.28)	0.217	0.12 (-0.02 to 0.23)	0.327	0.11 (-0.01 to 0.27)	0.401
	SBP CV	0.15 (0.05 to 0.26)	0.195	0.11 (-0.01 to 0.21)	0.313	0.10 (0.01 to 0.0.21)	0.374
	DPB SD	0.23 (0.09 to 0.39)	0.291	0.19 (0.03 to 0.34)	0.307	0.17 (0.02 to 0.33)	0.351
	DPB CV	0.19 (0.03 to 0.37)	0.277	0.15 (0.04 to 0.27)	0.295	0.15 (0.04 to 0.29)	0.283
Social cognition	SBP SD	-0.06 (-0.10 to 0.02)	0.571	-0.04 (-0.12 to 0.07)	0.653	-0.03 (-0.11 to 0.06)	0.692
	SBP CV	-0.05 (-0.09 to 0.04)	0.612	-0.02 (-0.13 to 0.11)	0.713	0.01 (-0.14 to 0.13)	0.865
	DPB SD	0.17 (0.08 to 0.27)	0.187	0.14 (-0.03 to 0.31)	0.295	0.13 (-0.02 to 0.29)	0.312
	DPB CV	0.16 (0.04 to 0.29)	0.203	0.13 (-0.01 to 0.30)	0.323	0.12 (-0.02 to 0.27)	0.371

Unadjusted model: Random intercept for the study center. Adjusted model 1: Corrected for age, education, and diabetes. Adjusted model 2: Corrected for age, education, diabetes, body mass index, hypertension, coronary artery disease, smoking, drinking, blood lipids, and serum creatinine levels. SBP SD: 24-hsystolic blood pressure standard deviation; SBP CV: 24-h systolic blood pressure coefficient of variation; DBP SD: 24-h diastolic blood pressure standard deviation; DBP CV: 24-h diastolic blood pressure coefficient of variation.

promoting oxidative stress and inflammation as well as neurodegeneration.

The results of this study show that BPV can be used as a tool to screen for early-stage cognitive decline; therefore, it is possible to delay or prevent further cognitive decline by improving BPV. The sample size of future studies should be increased and long-term follow-up assessments should be conducted to identify the correlation between BPV and cognitive impairment, especially in primary medical institutions as BPV can be considered a valuable tool for screening for cognitive decline.

This study had several limitations, including that it was a small cohort study and that participants were not randomly selected, which could potentially have biased the results. Other indicators that could have an impact on the results were not used in this study to measure BPV. Cerebrospinal fluid and PET tests were not performed, and variations in blood pressure and intracranial lesions could not be identified. Follow-up work should be carried out to extend the results of the study and determine whether effective control of BPV can reduce or reverse the decline in cognitive function. Effective control of BPV was not considered in this study.

CONCLUSION

According to this study, an increase in BPV is one of the risk factors for early cognitive decline. BPV was found to be

independently associated with SCD. BPV should be controlled effectively in clinical practice, especially in the treatment of hypertensive patients. The goal is not only to reach a standard blood pressure level but also to steadily reduce blood pressure and control BPV to better protect cognitive function and try to prevent or delay the occurrence of AD.

ARTICLE HIGHLIGHTS

Research background

Cognitive impairment is a highly harmful disease for which there is no perfect treatment. Early detection and treatment are the main focus of related research. Variation in blood pressure has been correlated with cognitive impairment in previous studies; however, few studies have examined subtle cognitive decline.

Research motivation

Our purpose was to analyze the influencing factors for subtle cognitive decline (SCD) and find a simple and effective index through which to assess cognitive decline that can be used to guide clinical work.

Research objectives

The study aimed to determine whether blood pressure variability (BPV) leads to cognitive impairment. The results showed that an increase in BPV is independently related to SCD and that BPV may be used as a tool for evaluating cognitive impairment and the effectiveness of treatment.

Research methods

We used a standard neuropsychological scale to evaluate cognitive function and retrospectively analyzed the correlation between BPV and SCD.

Research results

The results show that increased BPV may be a factor leading to cognitive decline. The results of such studies are rare; however, the sample size is not sufficiently large, and no further research has been carried out to determine whether it can be used as an index to analyze the effectiveness of treatment.

Research conclusions

This study demonstrates that BPV is a clinical indicator of early cognitive decline. In this study, 24-h ambulatory blood pressure monitoring test was used as an index from which to calculate BPV, one that is simple, effective, and can be readily used in primary healthcare institutions.

Research perspectives

Long-term follow-ups should be considered in the future to further the collective comprehension of the correlation between BPV and cognitive decline and the progress of cognitive impairment as well as to estimate the benefits of improving BPV in the treatment of cognitive impairment.

FOOTNOTES

Co-corresponding authors: Hui-Feng Guo and Yi Wu.

Author contributions: HF Guo and Y Wu analyzed the data and wrote the paper; Li J was responsible for execution and data collection; Pan FF was responsible for the study conception and design; the final version of the manuscript has been approved by all authors. Guo HF and Wu Y contributed equally to this work as co-corresponding authors. The reasons for designating them as co-corresponding authors are as follows: Firstly, this manuscript is a collaborative work. The designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. Secondly, Guo HF and Wu Y contributed equally to this work. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. Guo HF is responsible for the overall planning and the organization of clinical data, Wu Y is responsible for the data summary and statistical analysis. In summary, we believe that designating Guo HF and Wu Y as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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Independent risk factors for depression in older adult patients receiving peritoneal dialysis for chronic kidney disease

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Abstract

BACKGROUND

According to the trend of global population aging, the proportion of elderly patients with chronic kidney disease (CKD) is expected to increase. However, there are more than 20 million people in China with decompensated kidney function, of which 19.25% are elderly people. Therefore, special attention should be paid to the education years, sleep quality, anxiety status, comorbidities with diabetes, cardiovascular disease (CVD), and anemia as independent risk factors for depression in elderly CKD patients. This study explores the clinical management of elderly CKD patients that should address these risk factors to prevent depression and improve their prognosis.

AIM

To investigate depression risk factors in older patients receiving peritoneal dialysis, aiding future prevention of depression in these patients.

METHODS

This retrospective study included a primary study population of 170 patients with CKD who received peritoneal dialysis from January 2020 to December 2022. We assessed the patients' mental status using the Beck Depression Inventory Score-II (BDI-II), Self-Rating Anxiety Scale (SAS), Anxiety Inventory Score, and the Pittsburgh Sleep Quality Index (PSQI). Logistic regression was employed to identify depression independent risk factors among these patients.

RESULTS

The non-depressed group had a significantly longer education period than the depressed group ($P < 0.05$). The depressed group exhibited significantly higher mental status scores than the non-depressed group ($P < 0.001$). Patients with diabetes mellitus (DM) or CVD had a higher probability of developing depression. Patients with depression had significantly lower hemoglobin and albumin levels than patients without depression ($P < 0.05$). Spearman correlation

analysis of BDI-II scale scores, measuring depression, indicated positive correlations with BDI-II and SAS scores as risk factors for depression in patients with CKD. In contrast, years of education, hemoglobin levels, and peritoneal Kt/V were negatively correlated, serving as protective factors against depression. An analysis of variance for influences with significant differences in the univariate analysis revealed that years of schooling, BDI-II, SAS, PSQI, DM, CVD, and hemoglobin levels independently influenced depression in older patients with CKD.

CONCLUSION

Education, BDI-II, SAS, PSQI, DM, and CVD are independent risk factors for depression in older patients with CKD; therefore, post-treatment psychological monitoring of high-risk patients is crucial to prevent depression.

Key Words: Depression; Chronic kidney disease; Peritoneal dialysis; Older adults; Risk factors for depression; Beck Depression Inventory Score-II

Core Tip: We identified independent risk factors for depression in older patients with chronic kidney disease receiving peritoneal dialysis, including fewer years of education, higher Beck Depression Inventory Score-II and Self-Rating Anxiety Scale scores, poorer sleep quality, the presence of diabetes mellitus and cardiovascular disease, and lower hemoglobin and albumin levels. Conversely, more years of education, higher hemoglobin levels, and better peritoneal Kt/V ratio were associated with a lower risk of depression. These findings emphasize the importance of considering psychological well-being and addressing potential risk factors in the management of older patients on peritoneal dialysis, particularly in patients at high-risk of depression.

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INTRODUCTION

Chronic kidney disease (CKD), a severe condition, is associated with a group of syndromes and results from progressive kidney structure and function degradation over three months[1]. Patients with CKD exhibit clinical manifestations such as varying urinary protein levels, swelling, hypertension (HTN), and impaired kidney function[2]. Age significantly contributes to CKD, as kidneys decrease in size and lose with age[3]. In China, at least 20 million people have decompensated kidney function[4], with 19.25% being older adults. With global aging, the proportion of older patients with CKD is also likely to increase, necessitating special treatment and prognosis considerations.

Due to kidney shortages, CKD is often managed with renal replacement therapy, mainly hemodialysis and peritoneal dialysis[5]. Peritoneal dialysis utilizes the peritoneum as a semi-permeable membrane to remove dialysis fluid and metabolic waste[6]. Compared with hemodialysis, peritoneal dialysis is less expensive and has a lower ischemic effect on the kidneys, preserving residual function, and is more accessible[7]. However, CKD not only represents a financial burden to the patients but also leads to a rising rate of CKD-associated disabilities, causing patient suffering[8].

With advances in medical technology, the survival rates of patients with CKD is increasing, resulting in a growing population of patients with CKD[9]. Identifying means to improve their quality of life and prognosis has become a critical research focus. The prevalence of depression among patients with CKD is four times higher than that in the general population[10]. Among patients with CKD receiving ambulatory peritoneal dialysis, most often complain of poor sleep quality, moodiness, and lethargy, with a 58.1% prevalence of depression[11]. Despite variations in depression scales, ethnic groups, and geographic regions, various national and international studies have associated CKD-related depression to higher hospitalization rates, cardiovascular events, and suicide and mortality rates[12-14].

Based on the previous findings, this retrospective study explored the independent risk factors for depression in older patients with CKD receiving peritoneal dialysis to provide a scientific basis for reducing depression and improving the prognosis of older patients.

MATERIALS AND METHODS

Study participants and design

We selected 170 patients with CKD who received peritoneal dialysis treatment at the Cangzhou Central Hospital in the Hebei Province from January 2020 to December 2022. The study was approved by the ethics committee of the Cangzhou Central Hospital and all participants signed informed consent. The patient inclusion criteria were: (1) Age > 65 years; (2)

Met the diagnostic criteria for patients with CKD receiving peritoneal dialysis; (3) Ambulatory with unrestricted activity; and (4) No comorbid psychiatric conditions prior to observation and conscious and able to communicate autonomously. Patients were excluded if they had: (1) An emergency cardiovascular event with impaired consciousness; (2) other serious illnesses, such as cancer, myocardial infarction, and cerebrovascular accident (CVA); and (3) depression and anxiety before receiving peritoneal dialysis.

This retrospective study analyzed patients previously treated with peritoneal dialysis, collected their basic information and clinical data, and assessed their mental status using the Beck Depression Inventory Score-II (BDI-II), Self-Rating Anxiety Scale (SAS), Anxiety Inventory Score, and the Pittsburgh Sleep Quality Index (PSQI).

Clinical characteristics

Demographic information and prevalence data were collected from all participants. These data included age, sex, education level, body mass index (BMI), presence of HTN, presence of diabetes mellitus (DM), and history of cardiovascular disease (CVD). CVDs included coronary heart disease, congestive heart failure, myocardial infarction, and a history of CVA.

Laboratory methods

Peritoneal dialysis was continued after the patients were given a night meal. Venous blood was collected from all participants for routine blood tests. Blood tests were conducted using a fully automated chemistry analyzer (indicators included serum sodium, albumin, calcium, phosphate, cholesterol, and hemoglobin). Midmorning urine samples were collected to determine renal function. The total Kt/V and creatinine clearance of the patients' body after peritoneal dialysis were evaluated to determine the effectiveness of dialysis treatment.

Depressive state measurement

The BDI-II, SAS Anxiety Inventory Score, and PSQI scores were used to measure the depression status of the patients.

BDI-II: This scale assesses the degree of depression. It consists of 21 groups of items, with each group having four statements. Each question is scored from 0 to 3. Depression was classified as follows: patients with scores < 13 were considered non-depressed, 14–19 were considered mildly depressed, 20–28 were considered moderately depressed, and 29–63 were considered severely depressed[15].

SAS: This scale assesses the degree of anxiety. The standard SAS score has a cutoff of 50, with 50–59 indicating mild anxiety, 60–69 indicating moderate anxiety, and 70 or more indicating severe anxiety[16].

PSQI: This index is used to assess sleep quality over the last month. The total PSQI score ranges from 0 to 21. A negative correlation was observed between these scores and sleep quality (higher scores indicating poorer sleep quality). A score > 16 indicated poor sleep quality[17].

Statistical analysis

The data were processed using SPSS 26.0, with measurements expressed as the mean ± SD. Analysis of variance (ANOVA) or Student's *t*-test was performed to evaluate statistical significance. The *t*-test for independent samples was performed to compare the data between the two groups, and the chi-square test was performed to compare the count data in terms of composition ratio (%). Correlations were analyzed using the Spearman method, and influencing factors were analyzed using multiple linear regression models, with $P < 0.05$ considered as a statistically significant difference. Spearman's rank correlation was used to analyze the relationship between depression and each parameter, and logistic regression was performed to analyze the factors influencing depression.

RESULTS

Patient baseline characteristics

We collected demographic data and medical histories for analysis (Table 1). Among 170 patients, 59 were assessed as having depression based on the scale and clinical symptoms. Age, BMI, HTN, triglyceride, P, Ca, Na levels, and renal function did not significantly differ between the depressed and non-depressed groups ($P > 0.05$). However, a significant difference was observed in the length of education between the two groups ($P < 0.05$). The depressed group had significantly higher mental state scores compared to the control group ($P < 0.001$). Patients with DM and CVD were more prone to develop depression, and those in the depressed group had significantly lower hemoglobin and albumin levels than patients in the non-depressed group ($P < 0.05$).

Correlation between depression and relevant indicators in peritoneal dialysis patients

The results of the Spearman correlation analysis of BDI-II scale scores measuring depression with each factor revealed that BDI-II and SAS scores were positively correlated as risk factors for depression in patients with CKD. In contrast, years of education, hemoglobin levels, and peritoneal Kt/V were negatively correlated as protective factors against depression (Table 2).

Dichotomous logistic regression analysis of patient depression

ANOVA results revealed that years of schooling, BDI-II, SAS, PSQI, DM, CVD, and hemoglobin levels independently influenced depression in older patients with CKD (see Table 3 for indicator assignments) (Table 4).

Table 1 The baseline characteristics of the study patients

Factors	No-depression (*n* = 59)	Depression (*n* = 111)	*P* value
Age (yr, mean ± SD)	67.23 ± 0.23	68.11 ± 0.36	0.590
Sex (male/female)	78/33	41/18	0.975
BMI (kg/m^2, mean ± SD)	22.10 ± 0.55	20.83 ± 0.40	0.057
Year of education (yr)	8.0 ± 0.50	5.5 ± 0.50	0.021[1]
Mental State Scale scores			
BDI-II	5.72 ± 0.92	18.13 ± 0.21	< 0.001[3]
SAS	44.11 ± 1.02	60.92 ± 2.90	< 0.001[3]
PSQI	3.90 ± 0.67	19.02 ± 0.82	< 0.001[3]
Medical history			
HTN	21(35.59%)	41 (36.94%)	0.056
DM	35(59.32%)	56 (50.45%)	< 0.001[3]
CVD	12(20.33%)	24 (21.62%)	< 0.001[3]
Physical examination			
Albumin (g/L)	37.78 ± 0.41	31.27 ± 0.13	0.002[2]
Hemoglobin (g/L)	121.40 ± 11.90	103.90 ± 13.33	0.031[1]
Triglycerides (mmol/L)	1.98 ± 0.59	1.56 ± 0.46	0.072
P (mmol/L)	1.82 ± 0.35	1.74 ± 0.12	0.197
Ca (mmol/L)	2.34 ± 0.19	2.24 ± 0.26	0.237
Na (mmol/L)	137.25 ± 12.60	135.01 ± 15.06	0.892
Renal function			
Scr (μmol/L)	352.15 ± 15.65	350.21 ± 15.96	0.145
BUA (μmol/L)	369.78 ± 14.69	357.37 ± 14.34	0.774
Residual renal Kt/V	0.28 ± 0.09	0.26 ± 0.07	0.132
Peritoneal Kt/V	1.56 ± 0.10	1.54 ± 0.21	0.521

[1]$P < 0.05$.
[2]$P < 0.01$.
[3]$P < 0.001$.
HTN: Hypertension; DM: Diabetes Mellitus; CVD: Cardiovascular Disease; BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; Scr: Serum creatinine; BUA: Blood uric acid.

DISCUSSION

Because the older adult population comprises an increasing proportion of patients with CKD, improving their quality of life and prognostic outcomes has become a priority for their clinical management. Depression often results in reduced sleep quality and worry in older patients, which can lead to self-harm and, in severe cases, to suicidal behavior. Studies have evidenced that patients with CKD are more prone to depression than patients without CKD, possibly due to prolonged dialysis treatment and physical and psychological stress[18]. In this retrospective study, we analyzed cross-sectional data and the results revealed that indicators such as years of education and sleep quality are independent risk factors for depression in older patients with CKD.

Association between years of schooling and depression

Educational attainment has consistently been considered as a protective factor against depression. Our study reinforces this connection, revealing a significant negative correlation between that years of education and depression scores. Higher education often equates to lower depression rates associated to greater financial stability and access to health knowledge, fostering better acceptance of the patient's condition[19]. Moreover, the alleviating effect of education on depression increases with age[20]. Therefore, the protective effect of education on depression is more likely to be noted in the older adult population.

Table 2 Correlation between depression and relevant indicators in peritoneal dialysis patients

Factors	r_s	*P* value
Year of education	-0.415	< 0.001[3]
BDI-II	0.925	0.015[2]
SAS	0.982	< 0.001[3]
Hemoglobin	-0.332	0.002[2]
Peritoneal Kt/V	-0.456	0.023[1]

[1]*P* < 0.05.
[2]*P* < 0.01.
[3]*P* < 0.001.
BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale.

Table 3 Influencing factor assignments

Factors	Assignment
Years of schooling	> 6 yr = 0, < 6 yr = 1
BDI-II	< 14 score = 0, ≥ 14 score = 1
SAS	< 50 score = 0, ≥ 50 score = 1
PSQI	< 16 score = 0, ≥ 16 score = 1
DM	No = 0, yes = 1
CVD	No = 0, yes = 1
Albumin	≥ 35 = 0, < 35 = 1
Hemoglobin	< 110 = 1, ≥ 110 = 1

BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; DM: Diabetes Mellitus; CVD: Cardiovascular Disease.

Table 4 Dichotomous logistic regression analysis of patient depression

Indices	β	Wald	*P* value	OR	95% CI
Years of schooling	1.519	1.628	0.025[1]	0.971	0.921-0.987
BDI-II	0.116	5.177	< 0.001[3]	0.258	0.215-0.267
SAS	0.059	2.648	< 0.001[3]	1.605	1.420-1.700
PSQI	0.169	11.029	< 0.001[3]	0.157	0.144-0.162
DM	0.126	8.053	< 0.001[3]	1.264	1.201-1.274
CVD	0.236	2.615	0.002[2]	0.584	0.573-0.600
Albumin	-0.300	5.641	0.051	1.177	1.059-1.208
Hemoglobin	-0.321	3.641	< 0.001[3]	1.060	0.998-1.105

[1]*P* < 0.05.
[2]*P* < 0.01.
[3]*P* < 0.001.
BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; DM: Diabetes Mellitus; CVD: Cardiovascular Disease.

Studies have suggested that the education might strengthen the resilience of patients with CKD, reducing their susceptibility to depression. Our findings highlight that patients with lower educational levels are more prone to depression. In China, the majority of the older adults has a low education level, with a 13.90% of those aged ≥ 60 years having a high school education or higher as of 2021. This proportion may be even lower among older patients with CKD who have depression[21].

Association of sleep quality and anxiety with depression

Sleep quality and anxiety levels often conform with depression. Studies have reported that people experiencing poor sleep quality and higher anxiety levels are more likely to develop depression. This result is consistent with that of our study[22]. Sleep quality is crucial for health; however, older adults have significantly shorter sleep duration and generally poorer sleep quality than people from other age groups. From a neurobiological perspective, people with insomnia tend to exhibit increased activity in their arousal systems, leading to alterations in corticothalamic neural activity and neurotransmitter release. This includes the production of high levels of adrenocorticotropic hormones and cortisol, factors that increase susceptibility to mental health conditions such as depression and anxiety[23]. Sleep quality influences cognitive function as well as anxiety and depression in older adults. For example, Wang *et al*[24] found a significant association between sleep disturbance and depression scale and geriatric anxiety scale scores in Asian older adults. Therefore, monitoring sleep quality is crucial for the effective management of older patients with CKD.

Association of DM and CVD with depression

A large proportion of patients with Parkinson's disease develop diabetic nephropathy. A meta-analysis revealed a bidirectional association between diabetic nephropathy and depression. Similarly, a Japanese survey reported that the progression of diabetic nephropathy might increase the risk and severity of depression[25]. In cases of diabetic nephropathy, patients require long-term medication or insulin injections to control their blood glucose. Prolonged exposure to this disease can exacerbate depression. This depressive state may make patients less able to self-regulate and less aware of health protection, thereby exacerbating their overall medical condition, which can lead to progressive kidney failure.

Proteinuria is a risk factor of CVD. Advanced kidney disease can be exacerbated by CVD, leading to higher levels of depression[26]. Thus, a history of CVD is also a risk factor for depression in older patients with CKD[27]. The incidence of CVD tends to increase significantly with age; therefore, older patients with CKD are more likely to experience cardiovascular events that can exacerbate depression than the general population.

The relationship between anemia and depression

Anemia is a common complication in patients undergoing peritoneal dialysis and is caused by reduced erythropoietin production, toxin accumulation-induced erythropoietic depressants, shortened erythrocyte survival, and iron deficiency. Anemia is significantly associated with quality of life, CVD, hospital admissions, cognitive impairment, and death. In addition, patients with anemia often exhibit poor concentration and may also experience syncope and myocardial infarction, which can seriously affect their normal life and work[28]. Increased dyspnea and fatigue due to anemia may lead to a substantial decrease in physical and social activity, which in turn may increase depression. Hemoglobin and albumin levels serve as markers for anemia, and these two indicators were among the risk factors for depression in older patients with CKD, with a significantly higher incidence of depression in patients with anemia than in patients who did not present this condition.

Strengths and limitations

A strength of this study is its retrospective design, which enabled the analysis of independent risk factors associated with depression in older patients with CKD, providing a wider understanding of the patients' condition. Through correlation and logistic regression analyses, involving various factors associated with the incidence of depression in patients with CKD, the study compiled robust evidence, lending to more reliable results.

A limitation of this study is the absence of a comparative analysis involving other age groups. Therefore, the applicability of the study's findings is limited to the older adult population. However, at this stage, CKD patients are predominantly old. Although we believe that our findings can be generalized to other age groups, further studies are warranted to validate these hypothesis.

CONCLUSION

This study evidenced that years of education, sleep quality, anxiety status, comorbid DM, CVD, and anemia were independent risk factors for depression in older patients with CKD. Moreover, clinical management of older patients with CKD should address these risk factors to prevent depression and improve their prognosis.

ARTICLE HIGHLIGHTS

Research background

Previous studies demonstrated that over 20 million people in China experience decompensated kidney function, with 19.25% of them being older adults. Given the trend in global aging population, the proportion of older patients with chronic kidney disease (CKD) is expected to increase. Therefore, special attention should be focus on the treatment and prognosis of older patients with CKDs.

Research motivation

This study aimed to investigate the independent risk factors for depression in older patients with CKD undergoing peritoneal dialysis.

Research objectives

The study aimed to provide a clinical basis for the prevention of depression in older patients with CKDs.

Research methods

This retrospective study included a primary study population of 170 patients with CKD who received peritoneal dialysis from January 2020 to December 2022. We assessed the patients' mental status using the Beck Depression Inventory Score-II, Self-Rating Anxiety Scale, Anxiety Inventory Score, and the Pittsburgh Sleep Quality Index. Logistic regression was employed to identify depression independent risk factors among these patients.

Research results

The results of this study suggest that years of education, sleep quality, anxiety status, comorbid diabetes, cardiovascular diseases, and anemia are independent risk factors for depression in older patients with CKDs.

Research conclusions

This study found that years of education, sleep quality, anxiety status, comorbid diabetes mellitus, cardiovascular disease, and anemia were independent risk factors for depression in older patients with CKDs, and future clinical management of patients should address these risk factors to prevent depression and improve prognosis.

Research perspectives

This study investigated the independent risk factors for depression in older patients with CKD to provide a scientific basis for improving their prognosis, as well as to reduce the risk of depression in old age.

FOOTNOTES

Author contributions: Sheng YP, Ma XY, Liu Y, Yang XM and Sun FY designed the research; Sheng YP, Sun FY, Ma XY performed the research; Liu Y and Yang XM contributed new reagents/analytic tools; Sheng YP, Sun FY and Liu Y analyzed the data; Sheng YP, Sun FY and Ma XY wrote the paper.

Institutional review board statement: This study has passed the ethical review and approval of Cangzhou Central Hospital.

Informed consent statement: The study has obtained informed consent from the patient or the patient's guardian.

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ORIGINAL ARTICLE

Retrospective Study

Correlation analysis of mental health conditions and personality of patients with alcohol addiction

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Abstract

BACKGROUND

Alcohol addiction, or alcohol dependence, refers to a psychological state of strong craving for alcohol caused by drinking when both the drinking times and alcohol consumption reach a certain level. Alcohol addiction can cause irreversible damage, leading to mental illness or mental disorders, negative changes in their original personality, and a tendency to safety incidents such as committing suicide or violent attacks on others. Significant attention needs to be given to the mental health of alcohol addicts, which could reflect their abnormal personality traits. However, only a few papers on this issue have been reported in China.

AIM

To investigate the correlation between mental health and personality in patients with alcohol addiction.

METHODS

In this single-center observational study, we selected 80 patients with alcohol addiction as the research subjects, according to the criteria of the K10 scale to evaluate the mental health of patients with alcohol addiction, and divided these patients into four groups based on the evaluation results: Good, average, relatively poor and bad. And then analyzed the correlation between mental health conditions and personality characteristics from these four groups of patients.

RESULTS

The average score of the K10 scale (Kessler 10 Simple Psychological Status

Assessment Scale) in 80 patients with alcohol addiction was 25.45 points, the median score was 25 points, the highest score was 50 points, and the lowest score was 11 points. *Pearson*'s analysis showed that the K10 score was positively correlated with the scores of these two subscales, such as the P-subscale and the N-subscale ($P < 0.05$). In contrast, the K10 score had no significant correlation with the scores from the E-subscale and the L-subscale ($P > 0.05$).

CONCLUSION

The mental health conditions of patients with alcohol addiction are positively correlated with their personality characteristics.

Key Words: Alcohol addiction; Mental health; Personality characteristics; Public health; Patients; Correlational analysis

Core Tip: Alcohol addiction, as a special behavioral pattern, can cause serious mental and physical burdens, and therefore must be highly valued. This article aims to explore the correlation between the formation of alcohol addiction as a behavioral pattern and personality. By randomly grouping alcohol addicted patients and evaluating their mental health using the K10 scale, the results showed that the mental health status of alcohol addicted patients was positively correlated with their personality traits.

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INTRODUCTION

Alcohol addiction, or alcohol dependence, refers to a psychological state of strong craving for alcohol caused by drinking when both the drinking times and alcohol consumption reach a certain level. Alcohol addicts may get to the point of failing to control their drinking behavior, and a series of physical tolerance or withdrawal symptoms will appear[1]. These reactions will manifest as the patient's compulsive craving for alcohol. After the cessation of drinking behavior, some physical withdrawal symptoms may occur, such as palpitations, trembling, and dyspnea, or psychological withdrawal symptoms, such as anxiety, depression, and delusions of victimization. The above symptoms could disappear with the resumption of the drinking behavior[2]. Alcohol addiction is a disease that is difficult to cure, with a high prevalence rate and a high rate of relapse. According to data from the World Health Organization in 2018[3], approximately 237 million men and 46 million women worldwide suffered from alcohol dependence syndrome. The data shows that, in 2018, the annual drinking volume per capita in Chinese was 7.14 L, the annual drinking volume per capita in Northern American countries was 9.71 L, the annual drinking volume per capita in Western Europe countries was 11.13 L, and the yearly drinking volume per capita in Australia was 10.47 L. The proportion of heavy drinkers among China adults was 22.6%. The proportion of heavy drinkers among North American adults was 25.7%; among Western European adults was 30.5%; and among Australian adults was 34.4%[3].

According to the World Health Organization, health is defined as the absence of disease or being free of infirmity and the balanced and normal state of physical, psychological, and social[4]. Mental health is one of the most important public health issues in the world all the time. Psychological health, like physical health, can also affect the life quality of individuals; this fact should be prompting people to pay more attention to mental illness as to physical diseases[5]. Alcohol addiction can cause irreversible damage to the physical status, psychological conditions, and social adaptations of patients who suffer from it. It results in mental illness or mental disorders, causing negative changes in their original personality characteristics[6] and leading to vicious public safety incidents such as committing suicide or launching violent attacks on others. It is important to pay attention to the mental health of people with alcohol addiction.

Personality is the organic unity of the dynamic internal organization and the corresponding behavior patterns formed by individuals in various interactions. It is a complex structural system, mainly including two aspects; the tendency of personality and the rational characteristics of personality, the former is the driving force of personality, and the latter refers to the differences that exist among individuals[7]. In addition to physical damage like alcoholic liver disease, long-term heavy drinking can disturb their social adaptation and potentiate negative personality changes[8]. Alcohol addiction is strongly associated with personality disorders[9,10]. Personality disorders are considered important factors in the pathogenesis, persistence, and outcome of alcohol dependence in patients with these pernicious features[11].

The mental health condition of individuals is closely related to their personality characteristics. The mental health of alcohol addicts may reflect their unique but abnormal personality traits. However, at present, few related research has been reported in China. Based on this, this study aimed to investigate the correlation between mental health status and personality characteristics in people suffering from alcohol addiction.

MATERIALS AND METHODS

Research subject

In this single-centered observational study, we selected 80 patients with alcohol addiction treated in our hospital from January 2022 to January 2023 as the research subjects. And the inclusion criteria were the following: (1) Patients clinically diagnosed with alcohol addiction[12]; (2) The patient being aware and consciously participating in the investigation; and (3) The patient able to fill out the questionnaire independently or with the help of an investigator. Exclusion Criteria: (1) Patients with other serious illnesses that may affect their psychological condition (such as disability, cancer, *etc.*); (2) Patients with severe mental disorders that could impact affect the accuracy of the study; and (3) Those who are unwilling to cooperate with the investigation standards. All proceedings were carried out per the *Declaration of Helsinki*.

General demographic information questionnaire

The content of the questionnaire mainly included; (1) The basic personal information on alcohol addicts; their gender, age, marital status, education level, *etc.*; (2) The participants' financial situation, including the self-assessment of the financial level, whether they are autonomous, and whether they were indebted; (3) Daily life behaviors of patients, whether smoking, suffering from a sleep disorder, maintaining a good frequency of daily exercise, *etc.*; (4) The number of years set to the establishment of the alcohol addiction; and (5) Other related psychological conditions, including whether they had close friends to talk to, whether they encountered major setbacks or unfortunate situations, *etc.*

Mental health rating scale (K10)

The K10 scale[13], developed by Kessler and Mrocze of the University of Michigan, assesses patients' mental health and can screen for self-management scoring scales on the population's psychological status risk factors[14]. The scale is convenient to operate, owns the non-specific character in assessment, and has been widely used in the survey of mental health group in the United States, Canada, and other countries. The K10 scale contains ten items about anxiety, depression, and stress levels experienced in the last four weeks before the assessment. These are: (1) How often do you feel tired for no reason? (2) How often do you feel nervous? (3) How often do you feel nervous, and nothing else can calm you down? (4) How often do you feel hopeless about life? (5) How often do you feel uneasy and irritable? (6) How often do you feel restless and irritable so that it is difficult for you to calm down? (7) How often do you feel depressed? (8) How often do you feel strenuous when doing anything? (9) How often do you feel sad and nothing can interest you? and (10) How often do you you're your existence as meaningless? To each question corresponds five response criteria and scored in this manner; 5 points for "all time," 4 for "most of the time," 3 for "sometimes," 2 for "occasionally present," and 1 for "almost nonexistent." The total score is calculated according to the respondent's responses, with a score ranging from 10 to 50 points, where a maximum of 50 points could indicate that the patient has serious psychological distress, and a minimum score of 10, indicates that the patient has no psychological distress. This study was designed according to previous assessment criteria, and the overall score was classified into four levels: 10-19 points at the first level, which represented good mental health; level 2, 20-25 points, representing average mental health; level 3 score of 26-29, which represented relatively poor mental health; a score of 30-50 on a fourth scale represented bad mental health. The evaluation items of the K10 scale mainly focused on the two routine measurements such as anxiety and depression, which ascertain the degree of anxiety, depression, and life stress of the respondent during the previous four weeks and contribute to analyzing the population's mental health.

Eysenck personality questionnaire

Compiled by Eysenck in 1952, revised by Professor Gong Yaoxian in 1983, and formed a Chinese edition. The adult version of the questionnaire consists of four subscales, psychotropic (P), extrovert (E), neuroticism (N), and lie (L), with 88 questions[15]. Among them, psychopathic tendencies are reflected by the P dimension, introversion and extroversion are reflected by the introvert-E dimension, emotional stability is reflected by the N dimension, and the L tendency is used as an effectiveness scale. The P, E, N, and L scales include 23, 21, 24, and 20 items in the adult questionnaire, each of which only answers "yes" and "no," with 1 point per question. Among them, the introvert-E: A high score indicates that the person is extroverted, emotionally impulsive, adventurous, and good at interacting with people. A low score can indicate introversion, emotional stability, taciturn, indifference to people, quietness, introspection, and conformity. N: A high score would suggest depression, anxiety, preoccupation, emotional instability, and sometimes irrationality. Mental quality (P): High scores may indicate delayed reaction, being withdrawn and lazy, having no contact with anyone, being emotionally cold, poorly adaptable, eccentric and bizarre, and being incongruous with the environment. L: A high score indicates it is disguised and untrue. Disguise itself has a stable personality function related to various elements of other people. In this study, Cronbach's α of the P, E, N, and L subscales were 0.71, 0.78, 0.87, and 0.71, respectively.

Statistical analysis

SPSS22.0 statistical software was used to analyze and process data. Continuous variables were confirmed by the normality test and homogeneity test for variance, and it determined that they have the homogeneity of variance based on approximately normal distribution, expressed as mean ± SD, *t*-test, and ANOVA (analysis of variance). Categorical variables expressed as percentages, chi-square test, Fisher exact test or Mann-Whitney test, the correlation using *Pearson* correlation analysis, and taking the result of $P < 0.05$ to indicate that the difference was statistically significant.

Biostatistics statement: The statistical methods of this study were reviewed by the clinical research office from the corresponding author's institution prior to the submission.

RESULTS

General demographic information of patients with alcohol addiction

Eighty patients with alcohol addiction were included in this study, 67 male patients, 13 female patients, aged 20-65 years, and the duration of the addiction was 5-30 years. For other information (Table 1).

Analysis of mental health status of patients with alcohol addiction

The average K10 score of the 80 patients with alcohol addiction was 25.45, with a median score of 25, with the highest score being 50 and the lowest being 11. A score of K10 between 10 and 19 indicated that the patient's mental health was good (Grade 1, low risk of mental illness) in 17 people, accounting for 21.25%; A score of K10 on a score of 20-24 indicated that the patient's mental health status is average (Grade 2, low risk of mental illness), and there are 20 people in this group, accounting for 20.00%; A K10 score of 25-29 indicated that the patient's mental health is poor (Grade 3, higher risk of mental illness) in 32 people, accounting for 40.00%; A K10 score of 30-50 indicated that the patient's mental health is poor (Grade 4, high risk of mental illness) in 11 people, accounting for 13.75% (Table 2).

Analysis of personality characteristics of patients with alcohol addiction

The scores of the two subscales, including P-subscale and N-subscale in the 10-19 group, 20-24 group, 25-29 group, and 30-50 group of the K10 score, were statistically significant ($P < 0.05$). In contrast, the overall comparison of scores in E-subscale and L-subscale was not statistically significant ($P > 0.05$). Among them, the scores of the P-subscale were compared in the following groups, the 10-19 groups, and the 20-24 groups were smaller than the 25-29 groups and 30-50 groups, and the differences were statistically significant ($P < 0.05$). About the comparison in N-subscale scores, 10-19 groups < 20-24 groups < 25-29 groups, and 30-50 groups, and the differences were statistically significant ($P < 0.05$) (Table 3).

Correlation analysis of mental health conditions and personality characteristics

Pearson's analysis showed that the K10 score was positively correlated with the scores of the P-subscale, N-subscale, and other two subscales ($P < 0.05$). In contrast, the K10 score had no significant correlation with the scores of E-subscale and L-subscale ($P > 0.05$) (Table 4 and Figure 1).

DISCUSSION

Alcohol dependence, namely alcohol addiction, is a chronic and recurrent encephalopathy characterized by compulsive, intense cravings for alcohol, loss of control over alcohol use, and negative emotions and physical discomfort that will emerge when alcohol is unavailable. Harmful use of alcohol is one of the largest risk factors for death, disease, and disability[15-18]. The *Global Report on Alcohol Use and Health WHO in 2018* states that[3] in 2016, the global prevalence of alcohol use disorders (AUD) among people aged 15 and above reached 5.1%, and the prevalence of alcohol dependence in this age group reached 2.6%. The harmful use of alcohol caused approximately 3 million deaths worldwide in the same year, accounting for 5.6% of all deaths. According to the 2019 survey of Chinese groups of mental illnesses, the 12-month prevalence of AUD in China was 1.8%, and the lifetime prevalence was 4.4%, of which the 12-month prevalence of alcohol dependence was 0.7% and the lifetime prevalence was 1.3%[19]. Alcohol abuse can cause damage to multiple systems, including the nervous system, cardiovascular system, digestive system, respiratory system, *etc.* Long-term drinking can also cause the breakdown of family relationships, disturb normal work, and cause accidents after drinking that seriously endanger personal and social safety. Exploring the mechanisms of addiction in alcohol dependence, actively seeking new treatment options, and encouraging patients with alcohol dependent to receive professional treatment for alcohol withdrawal would be essential methods to reduce the harm due to alcohol abuse[20].

Addictive substances such as alcohol can activate the brain's reward system, and the reward hypothesis is a widely accepted neurobiological hypothesis of addiction[21]. The central nervous system can produce a rewarding effect on natural rewards, such as food, sex, *etc.*, thereby maintaining the continuity of the species. Almost all addictive substances can stimulate the brain's reward circuit, making it faster and more intense than natural rewards, resulting in intense pleasure in the individual. Positron emission tomography studies have shown that drunken doses of alcohol can promote the release of dopamine and opioid peptides from the brain to the ventral striatum, and rapid and high amounts of dopamine in the midbrain limbic system are associated with the subjective feeling of "hi," which is the rewarding effect [22]. Individuals associate alcohol use with positive rewards, which is positive reinforcement. The neurotransmitters and neuromodulators involved in alcohol reward include not only dopamine but also the opioid peptides, γ-aminobutyric acid, glutamic acid, serotonin, acetylcholine, and endocannabinoids acting on the ventral tegmental area or nucleus accumbens[23,24].

Patients with alcohol addiction are given to addictive substances, which greatly affect their mental health and personality characteristics. Jung[25] used the California Personality Questionnaire to implement the longitudinal measurement on adolescents who initially did not have drinking problems. Comparing boys who later developed drinking problems with the control group without similar issues, it was found that male alcohol addicts exhibited more rebellion and extroversion than others before they started drinking. While among female subjects, heavy drinkers showed more pessimism, introversion, and dependence as adolescents than light drinkers[25]. Cloninger *et al*[26] followed 431 subjects longitudinally for 16 years using a Three-dimensional Personality Questionnaire, which played an important role in clarifying the relationship between personality characteristics and alcohol abuse[26]. Cloninger *et al*[26] evaluated the

Table 1 The general demographic information of patients with alcohol addiction, *n* (%), mean ± SD

Variable	Number of cases (*n* = 80)	Constitution ratio (%)
Age		
< 50	47	58.75
≥ 50	33	41.25
Female	13	16.25
Man	67	83.75
Level of education		
Primary school and below	25	31.25
Junior high school and Senior high school	49	61.25
University and above	6	7.50
Marital status		
Married	51	63.75
Unmarried	9	11.25
Divorced or widowed	20	25.00
Self-evaluation of economic abundance		
Yes	31	38.75
No	49	61.255
Liabilities		
Yes	33	41.25
No	47	58.75
Smoking		
Yes	53	66.25
No	27	33.75
Sleep disorders		
Yes	46	57.50
No	34	42.50
Daily exercise		
Often	20	25.00
Sometimes	31	38.75
Never	29	36.25
The number of years set for getting ill		
≤ 5	24	30.00
6-10	34	42.50
≥ 11	22	27.50
Close friends		
Yes	28	35.00
No	52	65.00
Major setbacks or unfortunate situations		
Yes	57	71.25
No	23	28.75

Table 2 Analysis of mental health status of patients with alcohol addiction, *n* (%)

K10 Score	Number of cases	Percentage (%)
10-19	17	21.25
20-24	20	20.00
25-29	32	40.00
30-50	11	13.75
Total	80	100.00

Table 3 Analysis of personality characteristics of patients with alcohol addiction, mean ± SD

K10 scores	P	E	N	L
10-19 (n = 17)	6.34 ± 1.01[b,c]	7.51 ± 1.07	8.88 ± 2.72[a,b,c]	15.55 ± 2.31
20-24 (n = 20)	6.91 ± 1.40[b,c]	7.77 ± 2.06	11.84 ± 2.81[b,c]	15.18 ± 3.06
25-29 (n = 32)	8.98 ± 1.86	8.25 ± 1.91	14.72 ± 4.24	14.81 ± 3.47
30-50 (n = 11)	9.71 ± 1.67	8.42 ± 2.29	15.36 ± 2.11	15.61 ± 1.90
F	17.920	0.869	13.670	0.328
P value	< 0.001	0.460	< 0.001	0.804

[a]P < 0.05 comparison with the 20-24 groups.
[b]P < 0.05 comparison with the 25-29 groups.
[c]P < 0.05 comparison with the30-50 groups.
P: Psychotropic; E: Extrovert; N: Neuroticism; L: Lie.

Table 4 Correlation analysis of mental health conditions and personality characteristics

Item	*r* value	*P* value
P	0.477	< 0.001
E	0.201	0.074
N	0.454	< 0.001
L	-0.013	0.904

P: Psychotropic; E: Extrovert; N: Neuroticism; L: Lie.

participants' personality characteristics at 11 by behavioral assessment; Participants were then assessed for alcohol addiction at 27. The results showed that high sensation seeking and low harm avoidance were risk traits for alcohol addiction and that participants with these two traits in childhood were 20 times more likely to experience alcohol addiction in adulthood than those without these two traits. The thesis of De la Rosa-Cáceres *et al*[27] in 2022 noted that medium-to-high-risk personality characteristics in participants correlated with the diagnostic criteria for alcohol addiction[27]. Labouvie and McGee[28] conducted longitudinal studies of subjects aged 12 to 21 years, reaffirming that personality predicts alcohol and substance abuse and that adolescents with early substance abuse scored with a low degree on fulfillment, cognitive structure, and avoidance of harm but scored with a high degree on relationships, independence, depression, impulsivity, and play[28]. Gmel *et al*[29] analyzed the questionnaire results in 5125 young men and pointed out that high impulsivity and sensory seeking are also risk factors for alcohol addiction.

The results of this study showed that the K10 score of patients with alcohol addiction was positively correlated with the scores of two subscales such as P-subscale and N-subscale (r = 0.477, 0.518, 0.454, P < 0.05), patients with higher K10 scores had higher scores in P-subscale and N-subscale. The personality characteristics of those with high scores on the P-subscale presented social withdrawal trait, with strange behaviors like apathy and poor control. Herein, they responded strongly to various stimuli. People with high scores on N-subscale often have overt nervousness, fear, terror, irritability, restlessness, anxiety, depression, and panic; when these people encounter abnormal psychosocial problems, they are more difficult to extricate themselves than ordinary people and will be worried, depressed, and hesitant.

Alcohol-dependent patients with higher scores on P-subscale on the eysenck personality questionnaire (EPQ) score tend to have personality characteristics such as isolation, isolation, bizarre behavior, apathy, poor control, and therefore strong responses to various stimuli[30-32]. The reason may be that individuals who are withdrawn and introverted when

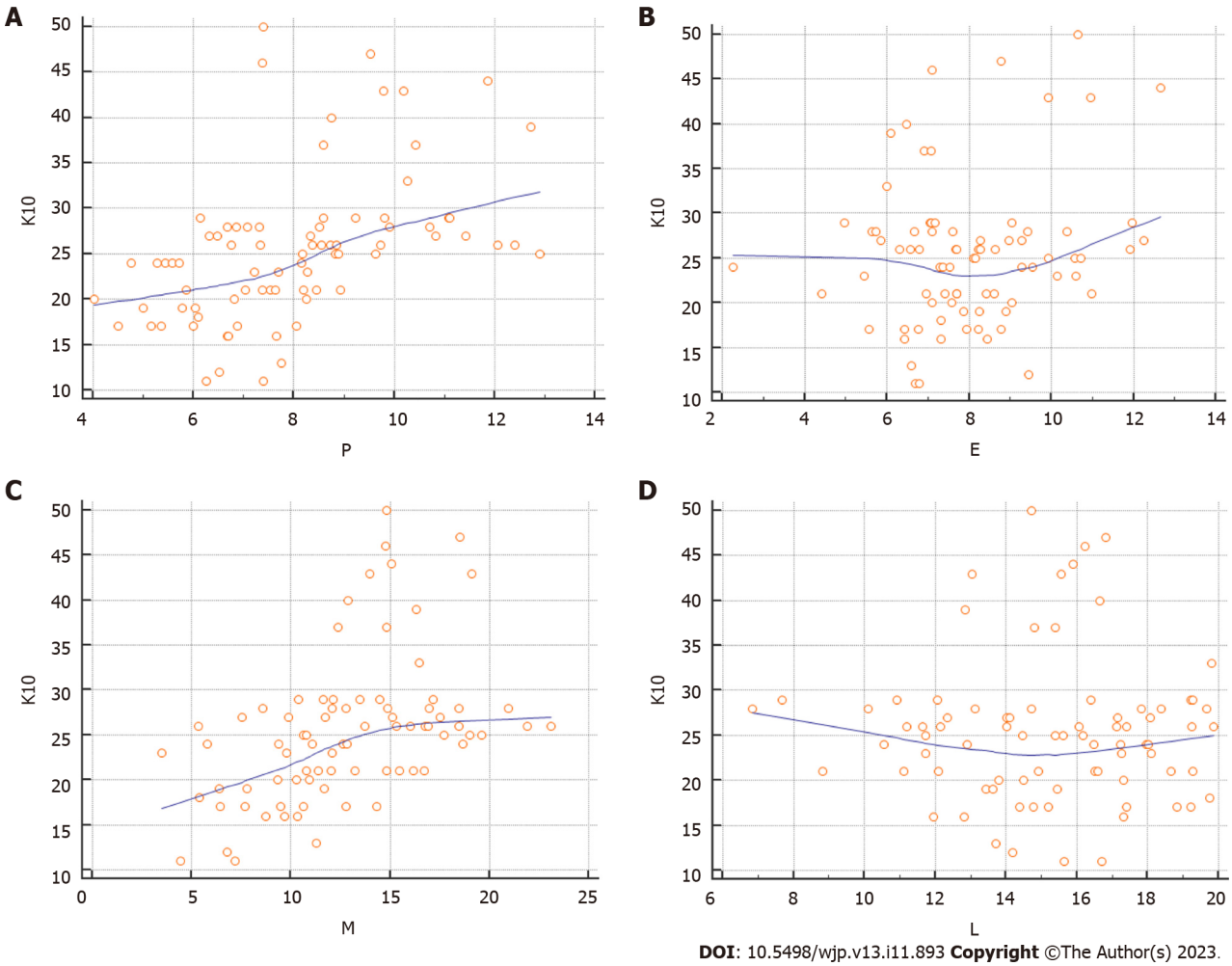

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Figure 1 The correlation between the K10 score and the subscale score. A: P-subscale score; B: E-subscale score; C: N-scale score; D: L-scale score. P: Psychotropic; E: Extrovert; N: Neuroticism; L: Lie.

they encounter unsatisfactory and unpleasant life events in daily life are neither good at alleviating their bad emotions by confiding inward troubles and depression to others, nor can they self-regulate through healthy and effective coping, so it is easier to apply the simple, direct but self-anesthesia method of drinking because of "Quench a thirst with poison" to avoid the bad reality, which is the so-called "Drinking can relieve thousands of worries." It might achieve certain results in the short term. Although individuals can also realize that long-term drinking could harm their bodies due to poor self-control. When they reencounter unsolvable life problems, they will involuntarily apply the so-called "effective" method as before, that is, "drinking." Consequently, they enter a vicious circle, increasing the possibility of "alcohol dependence." In addition, if the individual's sensitivity is high and it is easy to have a strong rational response to various stimuli, especially in the trivial matters of life, then it will be easier for them to all day long bothered by life dissatisfaction, which increases the possibility of "drinking" as a bad coping style. Moreover, patients with alcohol dependence due to long-term drinking habits will undergo certain changes. They will no longer care about their family, life, and work, having no emotional expression on their families and friends, just immersed in the "anesthesia" of alcohol all day. The general social interaction cannot interest them. Naturally, they will be like outliers and indifferent to anything. The patient will also have "foraging" behavior; that is, the patient will take all possible ways to find alcohol and meet the purpose of their drinking in the process of the patient's "foraging" in juncture to the conventional way. It may also include unconventional methods such as "Proposing a toast," "Cheating others to drink," "Gifting alcohol as private bribery," "Stealing alcohol," *etc.* these strange behaviors usually do not appear in normal individuals and represent the embodiment of "Weird behaviors."

Patients with alcohol dependence with higher N scores in the EPQ questionnaire had more obvious personality characteristics such as nervousness, fear, fear, irritability, restlessness, anxiety, depression, panic, anxiety, anxiety, depression, depression, and indecision[32-34]. The reasons could be that when individuals with tense, fearful, and indecisive personalities deal with life events, they are prone to cause difficulties in dealing with them correctly and in time due to their personality defects. When faced with choices in life, they will also miss the best time of choice and decision because of their indecision, so they might often fall into self-regret and afterward complain. Although individuals have also tried to apply healthy coping methods for solving problems, because of their nervous, fearful, and hesitant personality. These healthy coping styles are difficult to succeed in, so individuals will easily apply bad coping methods such as "drinking" to solve their adverse reactions. For individuals, "drinking" can not only solve the current dilemma in the short term, but

more importantly, it does not require too many personality characteristics and self-effort and successfully "avoids" the "negative influence" and "self-denial" brought about by their bad personality characteristics in the process of solving problems. Therefore, when individuals encounter similar life difficulties and other adverse conditions in the future, they will naturally use "drinking" to deal with it, which lays a certain foundation and conditions for forming later "alcohol dependence." In addition, if the individual's attitude to life is more negative, the individual is prone to be dissatisfied and disappointed with life and the future and will adopt more avoidance coping methods to deal with bad emotions and produce a sense of self "abandoned" by the world. At this time, the individual cannot solve his inner depression and resentment, and it is easy to use “drinking” to escape reality and self-anesthetize, and over time, the possibility of "alcohol dependence" will increase.

CONCLUSION

However, there were some limitations worth highlighting in this study. Firstly, the size of the sample studied was relatively smaller. And secondly, because this research was a single-center-based study, thus, the selection of these patients was limited to the scope of the patients in this hospital, which may have brought some biases in the interpretation of the results. Therefore, it appears necessary to design a larger, multi-center and multiethnic sample to further analyze and probe into the results of this study with an in-depth and sophisticated method.

ARTICLE HIGHLIGHTS

Research background

Correlation analysis of the correlation between alcohol addiction behavior and personality traits, exploring the causes of this behavior pattern, and thus serving the clinical treatment of alcohol addiction.

Research motivation

Alcohol addiction behavior is related to the personality characteristics of patients, and psychotropic (P) and neuroticism (N) dimensions of personality can positively induce alcohol addiction behavior.

Research objectives

There is a positive correlation between the scores of mental health assessment and the scores of P and N dimensions in personality assessment.

Research methods

Using the K10 Mental Health Assessment Scale, analyze the mental health status of alcohol addiction patients and its correlation with personality.

Research results

Based on existing research on the mental health of alcohol addiction, explore the correlation between the occurrence of alcohol addiction behavior and self-personality.

Research conclusions

Based on the existing talent gap of clinical research nurses, the training scheme of nurses should be scientifically customized to promote the development of clinical trials.

Research perspectives

Alcohol addiction, as a serious pattern of physical and mental harm, can lead to irreversible harm in severe cases. However, research reports on the causes of alcohol addiction behavior are not yet clear.

FOOTNOTES

Author contributions: Liu Y and Zhang XL contributed to the conceptualization; Liu Y and Cheng J performed the data curation; Pang LJ and Cheng J contributed to the formal analysis; Liu Y wrote the original draft; Zhang XL wrote the review and editing.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Anti-infective therapy durations predict psychological stress and laparoscopic surgery quality in pelvic abscess patients

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Abstract

BACKGROUND

The degree of psychological stress and the difficulty and efficacy of laparoscopic surgery differ in patients with pelvic abscesses after different durations of anti-infection treatment.

AIM

To compare and analyse the effects of different durations of anti-infective therapy on patients' preoperative psychological stress level and the clinical efficacy of laparoscopic surgery in patients with pelvic abscesses to offer a reference for the selection of therapy plans.

METHODS

A total of 100 patients with pelvic abscesses who were admitted to the Department of Gynecology of Suzhou Ninth Hospital affiliated to Soochow University (Suzhou Ninth People's Hospital) from January 2018 to December 2022 were retrospectively enrolled. According to the different durations of anti-infective therapy, they were divided into Group S (50 patients, received anti-infective therapy for 24-48 h) and Group L (50 patients, received anti-infective therapy for 48-96 h). Baseline data, state-trait anxiety score at admission and before surgery, self-rating anxiety scale (SAS) + self-rating depression scale (SDS) score, surgery time, adhesion grading score, intraoperative blood loss, presence or absence of intraoperative intestinal injury, ureteral injury or bladder injury, postoperative body temperature, length of hospital stay, and presence or absence of recurrence within 3 mo after surgery, chronic pelvic pain, incision infection, dysmenorrhea, menstrual disorder or intestinal obstruction were compared between the S group and the L group.

RESULTS

There was no significant difference in the background data between the S group

and the L group ($P < 0.05$). There was no significant difference in the state-trait anxiety score or SAS + SDS score between the S group and the L group on admission ($P < 0.05$). The state-trait anxiety score and SAS + SDS score of the S group were lower than those of Group L after receiving different durations of anti-infective therapy ($P < 0.05$). There was no significant difference in the incidence of intestinal, ureteral or bladder injury between the S group and the L group ($P < 0.05$). The surgery time of Group S was shorter than that of Group L, and the adhesion score and intraoperative blood loss volume were lower than those of Group L ($P < 0.05$). There was no significant difference in the incidence of incision infection, dysmenorrhea, menstrual disorder or intestinal obstruction between the S group and the L group ($P < 0.05$). The postoperative body temperature of Group S was lower than that of Group L ($P < 0.05$), and the hospital stay was shorter than that of Group L ($P < 0.05$). The incidences of recurrence and chronic pelvic pain within 3 mo after surgery were lower than that of Group L ($P < 0.05$).

CONCLUSION

Twenty-four to forty-eight hours of anti-infective therapy is better than 48-96 h of anti-infective therapy for patients with pelvic abscesses because the degree of psychological stress is lower, which is more conducive to achieving better outcomes after laparoscopic surgery.

Key Words: Anti-infective therapy; Pelvic abscesses; Psychological stress; Laparoscopic surgery; Efficacy

Core Tip: A pelvic abscess is a typical manifestation of pelvic inflammatory disease that can endanger the patient's life in severe cases. Here, we analysed the data of 100 patients with pelvic abscesses and divided them into Group S (anti-infective treatment for 24-48 h) and Group L (anti-infective treatment for 48-96 h) according to different durations of anti-infection. Through statistical analysis of the data of the two groups of patients, the authors researched the effects of different durations of preoperative anti-infective therapy on the psychological stress of patients and the postoperative effects of laparoscopic surgery in China to select the optimal duration of anti-infective therapy.

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INTRODUCTION

One of the most common serious infections in nonpregnant women of childbearing age is pelvic inflammatory disease (PID)[1]. PID is caused by mixed microbial infections of the upper reproductive tract, predominantly affects sexually active young women, and may be asymptomatic or present with tubuloovarian abscesses, which may be life threatening [2]. One of the most prevalent types of pelvic abscesses in women of childbearing age is tubo-ovarian abscesses. The best therapy for pelvic abscesses should be safe, effective, economical, minimally invasive, and have minimal effect on female fertility. Salpingo-ovarian abscesses have traditionally been treated with broad-spectrum antibiotics[3]. Long-term conservative therapy with drugs and long-term repeated use of antibiotics often lead to chronic pelvic abscesses or secondary adhesion, which decreases the patient's fertility, causes chronic pelvic pain, and seriously affects quality of life. Surgical intervention is required for patients who fail to receive conservative therapy. Except for a few patients with low-lying abscesses and a palpable posterior fornical incision and drainage tube, surgery has replaced conservative drug therapy and has become the first choice for the treatment of pelvic abscesses. Laparoscopic surgery has less biological impact on the body but a stronger protective effect on the immunity of the body, thereby reducing the incidence of infectious complications[4,5]. Preoperative anti-infective therapy can limit lesion development, prevent the spread of inflammation, and improve the efficacy of surgery. However, clinical observation shows that different durations of anti-infective therapy have different effects on surgery and postoperative outcomes. In our study, the data of 100 patients with pelvic abscesses who were admitted to our hospital in recent years were collected, and the differences in the outcomes of anti-infective therapy administered preoperatively, intraoperatively or postoperatively for different durations in patients with pelvic abscesses were analysed to find a more appropriate duration of anti-infective therapy.

MATERIALS AND METHODS

Patient characteristics

Data from a total of 100 patients with pelvic abscesses who were admitted to our hospital from January 2018 to December 2022 were retrospectively collected. According to different durations of anti-infective therapy, they were divided into

Group S and Group L. Group S was treated with anti-infective therapy for 24-48 h, and Group L was treated with anti-infective therapy for 48-96 h. There were 50 patients in Group S and 50 patients in Group L.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with pelvic abscesses that were diagnosed by symptoms, physical examination, ultrasound, routine blood examination and vaginal fornix puncture; (2) Patients undergoing elective laparoscopic surgery who were treated with sulperazon plus ornidazole for anti-infection treatment before surgery; (3) Patients who received anti-infective therapy and were evaluated with the state-trait anxiety[6], self-rating anxiety scale (SAS) and self-rating depression scale (SDS) scales[7]; and (4) Patients with complete data.

The exclusion criteria were as follows: (1) Patients with blood diseases or infectious diseases, who were pregnant or lactating, or with mental disorders or severe organ failure; (2) Patients with ruptured pelvic abscesses or who received other antibiotics before antibiotic therapy; and (3) Patients who refused to participate or had family members who were not supportive.

Patients and their relatives understood the content of our study and signed informed consent forms.

Methods

After the patients were diagnosed with pelvic effusion by examination, the Group S and the Group L were treated with sulperazon combined with ornidazole for anti-infective therapy; that is, according to the results of germ culture and drug sensitivity tests of puncture fluid, the patients were given 3.0 g sulperazon (H20020597; Pfizer Pharmaceuticals Co., LTD) and 0.25 g ornidazole (Hunan Jiudian Pharmaceutical Co., LTD). Both drugs were administered by intravenous drip twice every 24 h. Group S received 24-48 h of anti-infective therapy, while Group L received 48-96 h of anti-infective therapy. State-trait anxiety and SAS + SDS scores were obtained from both groups before and after admission.

After anti-infective therapy, laparoscopic surgery was performed in both groups. After general anaesthesia, the patient was intubated and mechanically ventilated to assist respiration, and the patient was placed in the head-down and bladder lithotomy position. After routine skin disinfection and skin draping, a 1 cm curved incision was made below the umbilical margin of the patient, and CO_2 pneumothorax was established with a pressure range of 10-12 mmHg. The laparoscope was placed in the abdomen, and surgery holes of 1 cm and 0.5 cm in size were cut at the left and right McHolley points of the lower abdomen, respectively. The exposed abscesses were incised, and pus and fragments were aspirated with an aspirator and sent to the laboratory. The surgical scope should be determined according to the patient's fertility requirements and the extent of the lesion and adjusted according to the patient's situation and needs. Patients with fertility requirements should undergo salpingostomy. After the surgery, normal saline and metronidazole solution were used to wash the pelvic cavity repeatedly, the patient's position was adjusted to head up and foot down, and the pelvic cavity was washed again. If the abscesses involved the fallopian tube, they were removed by bipolar coagulation, and haemostasis was performed. After abscess removal, the pelvis was flushed with 250 mL of 0.5% metronidazole solution, and a pelvic drainage tube was placed. According to the results of the germ culture and drug sensitivity test of abscess secretion, the corresponding antibiotics were given after the surgery. The body temperature was maintained at the normal level for 24 h. Then, oral antibiotics were administered for 1 to 2 wk.

Observation indicators

(1) The psychological stress of the patients in Group S and Group L was investigated by the scale at admission and before surgery. The state-trait anxiety score includes two parts: State anxiety (S-AI) and trait anxiety (T-AI). Each item is scored from 1 to 4 points, with positive emotions scored in reverse order. The total score of the S-AI and T-AI is 20 to 80 points. The higher the score, the higher the anxiety level. The SAS and SDS compiled by Zung[8,9] (the SAS/SDS self-rating scale includes 20 items, and each item is scored from 1 to 4; the higher the score, the greater the degree of psychological stress) were used to evaluate the patients; (2) Surgery time, adhesion score (the modified classification standard of adhesion of the American Society for Reproductive Medicine in 1996[10] was used to evaluate the extent, degree and nature of the adhesion during surgery), intraoperative blood loss, the presence or absence of intraoperative intestinal, ureteral and bladder injuries; and (3) Postoperative body temperature, length of hospital stay, and the presence or absence of recurrence within 3 mo after the surgery, chronic pelvic pain, incision infection, dysmenorrhea, menstrual disorder, or intestinal obstruction.

Statistical procedure

SPSS 26.0 was used for statistical analysis. Measurement data are expressed as the mean ± SD, and a *t* test was used. Count data are expressed as a percentage (%), the χ^2 test was used, and $P < 0.05$ was regarded as statistically significant.

RESULTS

The difference in baseline data

There was no significant difference in age, sex, body temperature, mass diameter or reproductive history between Group S and Group L ($P > 0.05$). As shown in Table 1.

The difference in psychological stress

There was no significant difference in the state-trait anxiety score or SAS + SDS score between the Group S and the Group

Table 1 Comparison of baseline data between the S group and the L group

Baseline data	Group S (*n* = 50)	Group L (*n* = 50)	t/χ^2	*P* value
Age (mean ± SD)	32.2 ± 4.1	33.9 ± 5.3	1.794	0.076
Duration disease (mo, mean ± SD)	14.7 ± 3.2	15.4 ± 2.9	1.146	0.255
Body temperature (°C, mean ± SD)	37.5 ± 1.5	37.7 ± 1.3	0.713	0.478
Diameter of mass (cm, mean ± SD)	5.9 ± 1.9	6.3 ± 1.6	1.139	0.258
Reproductive history [*n* (%)]	46 (82)	43 (86)	0.919	0.338

L at admission ($P > 0.05$). The state-trait anxiety score and SAS + SDS score of Group S were significantly lower than those of Group L after 24-48 h and 48-96 h of anti-infective therapy ($P < 0.05$) (Figure 1).

Differences in intraoperative clinical indicators

There was no significant difference in the incidence of intestinal, ureteral and bladder injuries between the Group S and the Group L ($P > 0.05$). The surgery time of Group S was shorter than that of Group L, and the adhesion score and intraoperative blood loss were lower than those of Group L ($P < 0.05$). As shown in Table 2 and Figure 2.

The difference in postoperative efficacy

There was no significant difference in the incidence of postoperative incision infection, dysmenorrhea, menstrual disorder, or intestinal obstruction between the Group S and the Group L after different durations of anti-infective therapy ($P > 0.05$). Postoperative body temperature was lower in Group S after 24-48 h of anti-infective therapy than in Group L after 48-96 h of anti-infective therapy ($P < 0.05$), and the hospital stay was shorter than that of Group L ($P < 0.05$) (Figure 3). The incidences of recurrence and chronic pelvic pain within 3 mo after surgery in Group S were lower ($P < 0.05$) than that in Group L (Table 3).

DISCUSSION

In the past, pelvic abscesses were often treated with conservative drug therapy[11], that is, long-term repeated use of antibiotics, because antibiotic therapy alone was not only ineffective in achieving a complete cure but could also cause the disease to develop into chronic PID or chronic pelvic abscesses, leading to secondary pelvic adhesion[12]. Therefore, surgery gradually replaced conservative therapy to become the main therapy method. In laparoscopic surgery, the advantages are the small incision, sufficient surgical field, no unnecessary interference, no exposure of abdominal organs to the air, less interference with the pelvic environment, less intraoperative blood loss, and fewer complications[13]. However, a pelvic abscess is an inflammatory reaction caused by a pathogenic bacterial infection. If surgical therapy is carried out directly after diagnosis, it is easy for inflammation to spread and affect the surgical outcome. Preoperative anti-infective therapy can control the spread of systemic inflammation, relieve pelvic abscesses, and facilitate a smooth course of surgery. However, there is no consensus on the optimal duration of preoperative anti-infective therapy.

In our study, the incidences of intraoperative injury and postoperative complications in Group S were lower than that in Group L, but the difference was not statistically significant, which may be related to the small sample size and individual differences between patients. However, the state-trait anxiety score and SAS + SDS score of Group S were statistically lower than those of Group L ($P < 0.05$), indicating that patients who received 24-48 h of anti-infective therapy had less preoperative psychological stress than those who received 48-96 h of anti-infective therapy. This may be because a long duration of preoperative anti-infective therapy diminishes patients' expectations for surgery or because patients have a misunderstanding of their illness. Stevens *et al*[14] showed that the higher the patients' preoperative expectations for surgery, the higher their depression and anxiety scores. Therefore, we speculated that with a prolonged anti-infection treatment time, patients' expectations of the operation effect increased, and they were more likely to have anxiety, depression and other psychological conditions. The study by Kılıç *et al*[15] showed that the longer the treatment time, the heavier the patients' psychological burden. According to this, we believe that a longer period of anti-infection treatment may make patients with pelvic abscesses think that preoperative preparation is not sufficient, their physical weakness cannot withstand the surgical trauma, or their disease will be suddenly worsened, thus causing them to experience worry, anxiety, depression and other adverse emotions. Therefore, we suggest that surgeons pay attention to patients who have undergone anti-infection treatment for an extended period before surgery or have anxiety and depression to be able to provide certain preoperative psychological education if necessary. However, after reviewing a large number of studies, we did not find any correlation between preoperative anti-infective treatment time and preoperative psychological state in patients with pelvic abscesses. Therefore, the specific relationship between preoperative anti-infective treatment time, psychological stress effect and surgical effect in patients with pelvic abscesses needs to be further investigated.

After 24-48 h of anti-infective therapy, the surgery time, adhesion score, intraoperative blood loss volume, postoperative body temperature was significantly lower and the hospital stay was significantly shorter in Group S than those in Group L ($P < 0.05$), indicating that compared with 24-48 h of anti-infective therapy, long-term anti-infective

Table 2 Comparison of intraoperative clinical indicators

Clinical indicators	Group S (n = 50)	Group L (n = 50)	t/χ^2	P value
Surgery time (min)	55.45 ± 16.48	78.78 ± 17.87	2.714	< 0.01
Adhesion score	3.17 ± 0.84	4.04 ± 0.49	6.326	< 0.001
Intraoperative blood loss (mL)	45.54 ± 11.94	72.15 ± 9.21	12.48	< 0.001
Intraoperative intestinal injury	1 (2.00)	3 (6.00)	1.042	0.307
Intraoperative ureteral injury	2 (4.00)	6 (8.00)	2.174	0.140
Intraoperative bladder injury	0 (0.00)	2 (4.00)	2.041	0.153

Table 3 Comparison of efficacy

Indicators	Group S (n = 50)	Group L (n = 50)	t/χ^2	P value
Postoperative body temperature	38.02 ± 0.98	38.94 ± 1.37	3.862	< 0.001
Length of stay (d)	7.68 ± 1.41	9.94 ± 2.01	6.509	< 0.001
Tumour recurrence within 3 mo after surgery	1 (2.00)	8 (6.00)	5.983	0.014
Chronic pelvic pain	2 (12.00)	12 (20.00)	8.306	0.004
Incision infection	0 (0.00)	3 (6.00)	3.093	0.079
Dysmenorrhea	5 (10.00)	11 (22.00)	2.679	0.102
Menstrual disorders	2 (4.00)	4 (8.00)	0.709	0.4
Intestinal obstruction	0 (0.00)	1 (2.00)	1.01	0.315

therapy is more likely to produce abdominopelvic adhesion[16]. Adhesions occur in 60% to 90% of gynaecological patients after abdominal pelvic surgery[17], and fibrous connections connecting tissue surfaces at abnormal locations can lead to chronic pelvic pain, infertility, intestinal obstruction, and the need for a complex reoperation[18-20]. In addition, it was found that in patients with long-term anti-infective therapy who underwent laparoscopic surgery, the abdominopelvic adhesion was more serious, the adhesion range was large, and the adhesion was dense, making it difficult to separate and a hindrance to surgery. The reason may be that 24-48 h after anti-infective therapy, the pelvic lesions are mainly composed of inflammatory exudate, and the membranoid adhesion is loose and easy to separate, which is more conducive to the surgery and thus to the postoperative effect. After 48-96 h of anti-infective therapy, inflammatory exudate on the surface of various organs of the patient's body can organize to form fibrin-like adhesion bands. Inflammatory exudates and tissue adhesions with increased density are hindrances to surgery and increase the incidence of postoperative complications. In addition, according to the above findings, we speculate that a smooth course of laparoscopic surgery and its increased efficacy after 24-48 h of anti-infective treatment may be related to the lower degree of psychological stress of patients before surgery. Ki *et al*[21] showed that compared with patients without anxiety before surgery, patients with anxiety before surgery had worse postoperative recovery quality. The researchers noted that anxiety before surgery can affect the quality of physical and mental recovery after surgery. In addition, Park *et al*[22] confirmed that anxiety and depression had a negative impact on the clinical outcome of rotator cuff repair. For the results of this study, we believe that a short period of anti-infection treatment before surgery can reduce the degree of psychological stress of patients before surgery and relieve anxiety and depression to promote a smooth operation and improve its curative effect. However, our views are limited to the research centre and the study population, thus it is necessary to expand the research scope to enhance the reliability of the results of this study.

The data showed that in addition to pelvic pain and incision infection, there were complications such as injury to the surrounding organs in the Group S and the Group L after the surgery, and the incidence of dysmenorrhea was higher, which was mainly related to the difficulty of separation of a thick-walled abscess or the difficulty of removing inflammatory exudates on the surface of organs[23,24]. In addition, surgery may also be one of the reasons for a high incidence of complications. Laparoscopic operators should be aware of potential complications and how to prevent them, strictly adhere to the surgical indications during therapy and learn how to identify complications early to deal with them safely and effectively. In cases of difficult surgery, experienced surgeons are better suited to operate[25,26].

However, our study still has some limitations: (1) The patient data were collected from a single centre, making extrapolation difficult; (2) it is a retrospective study, and the results of our study can only offer recommendations, thus future prospective studies are needed to verify the research findings; and (3) The sample size was small, and there was considerable bias, so a large sample study is still needed to verify the conclusion.

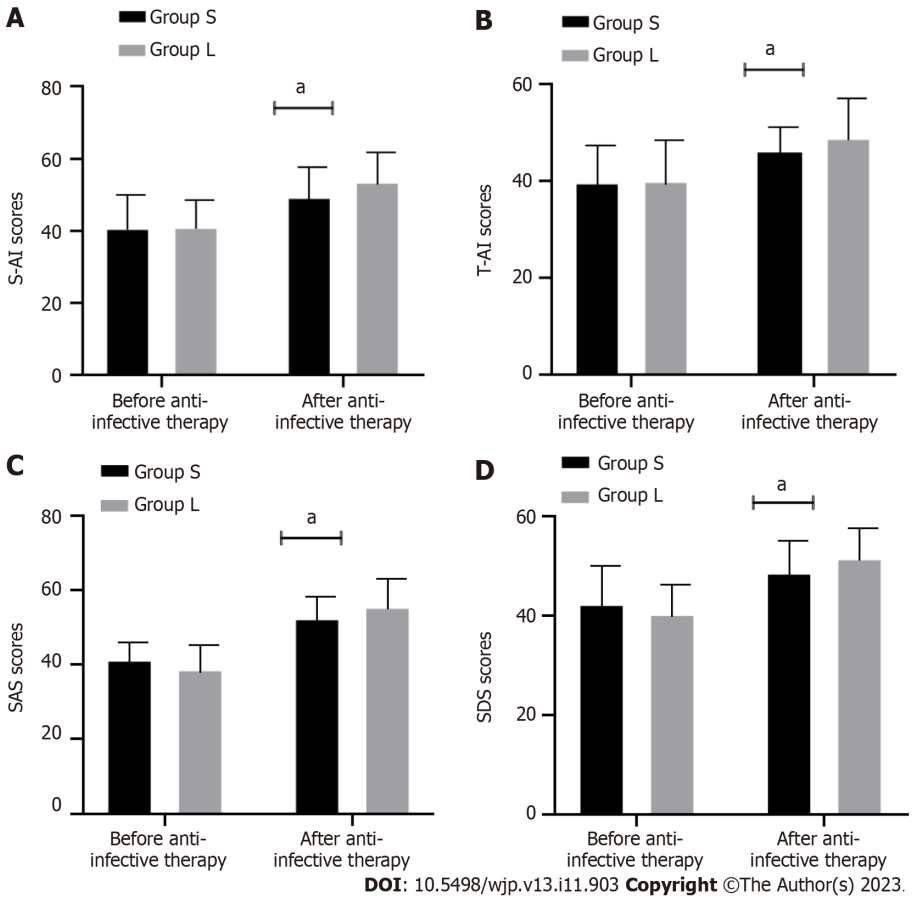

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Figure 1 The difference in psychological stress. A: State anxiety score (SAS) before and after anti-infective therapy; B: Trait anxiety scores before and after anti-infective therapy; C: Self-rating anxiety scale scores before and after anti-infective therapy; D: Self-rating depression scale (SDS) scores before and after anti-infective therapy. Data are expressed as the mean ± SD. The state-trait anxiety score and SAS + SDS score of Group S were significantly lower than those of Group L after 24-48 h and 48-96 h of anti-infective therapy. S-AI: state anxiety; T-AI: trait anxiety; SAS: self-rating anxiety scale; SDS: self-rating depression scale. [a]*P* < 0.05, there is significant difference between group S and group L after anti-therapy.

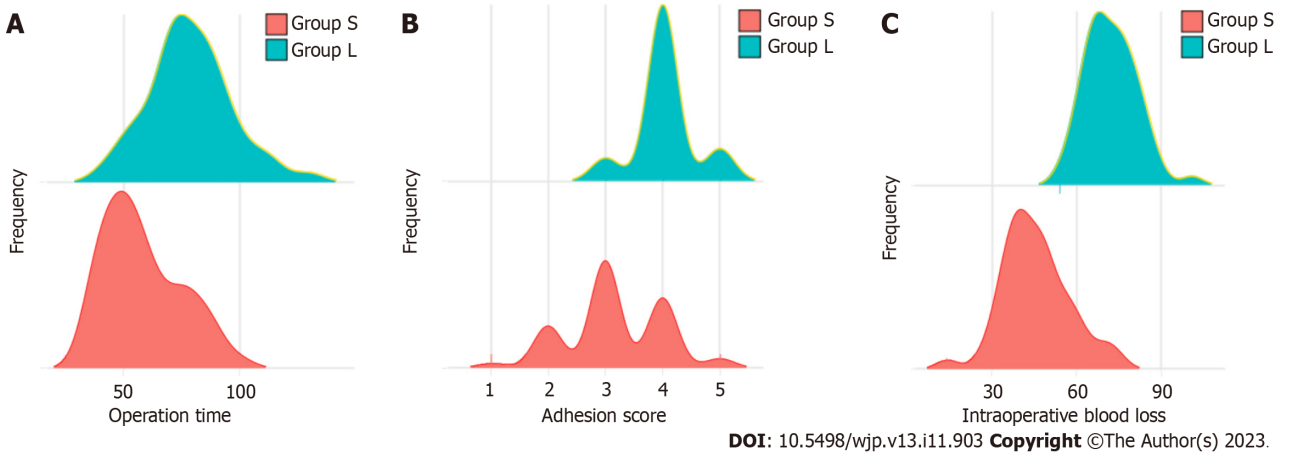

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Figure 2 Operation time, adhesion score, and intraoperative blood loss of the two groups. A: Operation time; B: Adhesion score; C: Intraoperative blood loss. The surgery time of Group S was shorter than that of Group L, and the adhesion score and intraoperative blood loss were lower than those of Group L (*P* < 0.05).

CONCLUSION

Compared with 48-92 h, 24-48 h of anti-infective therapy followed by laparoscopic surgery for pelvic abscesses is associated with less psychological stress in patients, is more conducive to surgery, and increases surgical efficacy.

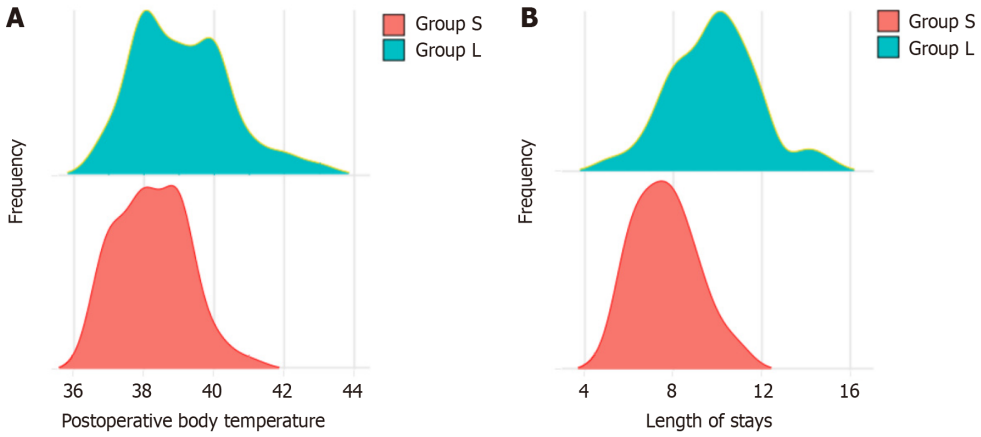

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Figure 3 Postoperative body temperature and length of stay of the two groups. A: Postoperative body temperature; B: Length of stay. Postoperative body temperature was lower in Group S after 24-48 h of anti-infective therapy than in Group L after 48-96 h of anti-infective therapy ($P < 0.05$), and the hospital stay was shorter in Group S than in Group L ($P < 0.05$).

ARTICLE HIGHLIGHTS

Research background

Pelvic abscess is a serious pelvic inflammatory disease (PID). It can be caused by a variety of factors, including surgery (*e.g.*, low anterior resection), pelvic visceral perforation, diverticulitis, appendicitis, ischaemic colitis, inflammatory bowel disease, or PID.

Research motivation

Different durations of anti-infective therapy have different effects on patients' psychological state, the difficulty of laparoscopic surgery and surgical efficacy.

Research objectives

The aim of this study was to determine the optimal duration of preoperative anti-infective therapy in patients with pelvic abscesses.

Research methods

This study retrospectively analysed the differences in preoperative psychological stress, intraoperative operation difficulty and postoperative recovery of patients with pelvic abscesses after different durations of anti-infection treatment.

Research results

Among the 100 patients with pelvic abscesses, the patients who received 24-48 h of anti-infection treatment had less preoperative psychological stress, less intraoperative operation difficulty and better postoperative recovery than those who received 48-96 h of anti-infection treatment.

Research conclusions

Through observation, we put forward the theory that 24-48 h of anti-infection treatment is better than 48-96 h of anti-infection treatment for patients with pelvic abscesses undergoing laparoscopic surgery.

Research perspectives

The different effects of anti-infection treatment on patients' preoperative psychological stress and the difficulty and efficacy of laparoscopic surgery in patients with pelvic abscesses were observed.

FOOTNOTES

Author contributions: Zhang RR and Zhao RH conceived and designed the study; Zhang RR and Zhang L guided the study; Zhang RR and Zhao RH collected the clinical date; Zhang RR and Zhao RH analyzed the data; All authors drafted and revised the manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Suzhou Ninth Hospital affiliated to Soochow University (Suzhou Ninth People's Hospital).

Informed consent statement: All study participants or their legal guardians provided informed written consent prior to study enrolment.

Conflict-of-interest statement: All authors declare that there are no conflicts of interest.

Data sharing statement: The data for this study can be obtained from the corresponding author upon request.

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ORIGINAL ARTICLE

Retrospective Study

Correlation study between motor rehabilitation level and psychological state in patients with limb movement disorders after stroke

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Abstract

BACKGROUND

The psychological state of patients with post stroke limb movement disorders undergoes a series of changes that affect rehabilitation training and recovery of limb motor function.

AIM

To determine the correlation between motor rehabilitation and the psychological state of patients with limb movement disorders after stroke.

METHODS

Eighty patients with upper and lower limb dysfunction post stroke were retrospectively enrolled in our study. Based on Hospital Anxiety and Depression Scale (HADS) scores measured before rehabilitation, patients with HADS scores ≥ 8 were divided into the psychological group; otherwise, the patients were included in the normal group. Motor function and daily living abilities were compared between the normal and psychological groups. Correlations between the motor function and psychological status of patients, and between daily living ability and psychological status of patients were analyzed.

RESULTS

After 1, 2, and 3 wk of rehabilitation, both the Fugl-Meyer assessment and Barthel index scores improved compared to their respective baseline scores ($P < 0.05$). A greater degree of improvement was observed in the normal group compared to the psychological group ($P < 0.05$). There was a negative correlation between negative emotions and limb rehabilitation ($-0.592 \leq r \leq -0.233$, $P < 0.05$), and between negative emotions and daily living ability ($-0.395 \leq r \leq -0.199$, $P < 0.05$).

CONCLUSION

There is a strong correlation between motor rehabilitation and the psychological state of patients with post stroke limb movement disorders. The higher the negative emotions, the worse the rehabilitation effect.

Key Words: Stroke; Limb movement disorders; Motor rehabilitation; Psychological state; Correlation

Core Tip: Stroke, also known as a cerebrovascular accident, is characterized by an acute and rapid onset and is the most common cerebrovascular disease. Stroke can cause limb dysfunction, resulting in functional limitations. Some people may experience a series of changes in their psychological state after illness, which affects rehabilitation training and recovery of limb function. The results of this study showed a strong correlation between the recovery of limb function with rehabilitation and psychological state of stroke patients. Therefore, it is necessary to pay close attention to psychological changes during rehabilitation, and implement timely adjustments and interventions for future rehabilitation.

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INTRODUCTION

Stroke can be subdivided into cerebral hemorrhage and cerebral infarction[1]. It is a clinical emergency that causes ischemic damage to the brain tissue due to the blockage or sudden rupture of small- and medium-sized blood vessels in the brain. According to the most recently published statistics, stroke ranks first as the leading cause of mortality in China, and is the main cause of accidental deaths, except for car accidents and falls from high altitudes[2]. Patients with stroke may experience swallowing and limb dysfunction, and in severe cases, they may lose their ability to take care of themselves, increasing the burden on their families and taking a serious negative toll on their mental health and resilience [3]. Therefore, it is necessary to pay close attention to psychological changes during rehabilitation, and implement timely adjustments and interventions for future rehabilitation and restoring the patient's quality of life.

The current medical disease model incorporates biological, psychological, and social factors. Medical workers should shift their treatment methods from traditional treatments to biological, psychological, and social models[4]. As the patient is anxious and worried when seeking medical treatment, the complex psychological effects can have pathogenic consequences[5]. Therefore, we should pay attention to the patients' psychological states, carefully observe their psychological reactions, and implement targeted psychological interventions based on their characteristics[6]. Related studies have shown that psychological interventions can reduce anxiety, depression, and fear in patients by reducing the heart rate, blood pressure, and catecholamine levels in blood and urine, and alleviate tension during exercise[7]. It can inhibit the activity of nociceptive neurons in the central area of the cerebral cortex, reduce their excitability, increase the pain threshold, and alleviate pain[8].

According to previous reports, there is a correlation between recovery and psychological state of the patient[9]. The better the patient's psychological state, the better will be their limb function recovery, and their quality of life will also improve accordingly[10]. This article mainly studied the correlation between the recovery of limb function owing to rehabilitation and psychological resilience in elderly stroke patients to provide a reference for psychological nursing and quality of life intervention in elderly stroke patients.

MATERIALS AND METHODS

Patient characteristics

Eighty patients with limb dysfunction after stroke who were admitted to the First Affiliated Hospital of Henan University of Science and Technology from May 2022 and May 2023 were retrospectively selected. The inclusion criteria were as follows: (1) A confirmed diagnosis of stroke on head computed tomography or magnetic resonance imaging according to

the diagnostic criteria proposed by the American Heart Association/American Stroke Association for stroke[11]; (2) The course of treatment is more than 21 d, and the condition is stable without recurrence; (3) The patient has a clear sense of autonomy and good cognitive ability; and (4) Patients with limb dysfunction after stroke. The exclusion criteria included: (1) Other serious cardiovascular and cerebrovascular diseases; (2) Patients with malignant tumors; (3) Patients with mental illness; (4) Patients with unstable vital signs; (5) Patients with previous stroke but residual upper and lower limb dysfunction and other sequelae; and (6) Patients with a history of surgery, fractures, arthritis, or pain that affects the recovery of upper and lower limb function. Based on the Hospital Anxiety and Depression Scale (HADS) scores before the start of rehabilitation, the patients were divided into the psychological group (those with HADS scores ≥ 8) and the normal group (those with HADS scores < 8).

Evaluation indices

The HADS index was used to evaluate the psychological state of patients[12]. This is a 14-item scale with seven items rated as anxiety and seven items rated as depression. If the HADS score is ≥ 8, it indicates symptoms of anxiety and depression. If the HADS score is < 8, the patient's psychological state is considered normal.

The Fugl-Meyer assessment (FMA) was used to evaluate the patient's upper and lower limb motor function[13]. There were 50 items with a total maximum score of 100 points. The upper limb score consists of 33 items and 66 points. The lower upper limb score consists of 17 items and with a total of 34 points.

The Barthel index (BI) for activities of daily living[14] was used to assess the patients' daily living abilities. The BI includes 10 items, with a total of 100 points. Except for walking on flat ground and bed-to-chair transfer, the full score was 15 points, whereas the full score for grooming and bathing was 5 points. The remaining items had a total score of 10 points.

Statistical analysis

SPSS 20.0 was used to statistically analyze the data. The measurement data were represented by (mean ± SD), and the *t*-test was used for intergroup comparisons. The counting data is represented in the form of percentage, and χ^2 is used for the intergroup comparisons. Pearson's correlation analysis was used to analyze the relationship between the rehabilitation of limb function and the psychological status of patients as well as the relationship between daily living ability and psychological status. Statistical significance was set at $P < 0.05$.

RESULTS

The comparison of general data

As shown in Table 1, there were no differences between gender (male, 60% *vs* 62.5%), age (65.33 ± 4.59 *vs* 65.90 ± 4.91), body mass index (25.43 ± 2.08 *vs* 25.86 ± 1.74), and course of disease (27.93 ± 7.11 *vs* 27.83 ± 7.88) between the normal and psychological groups ($P > 0.05$). The results showed that most stroke patients with motor disorders were classified as elderly and the duration of the disease was between 1 and 2 mo.

The comparison of motor function between normal and psychological groups

As shown in Figures 1A and B, there was no difference in the FMA scores of the upper and lower limbs between the normal and psychological groups ($P > 0.05$). After 1, 2, and 3 wk of rehabilitation, the FMA scores of the upper and lower limbs improved in both groups ($P < 0.05$). In addition, the FMA scores of the upper and lower limbs in the normal group had more substantial improvement than those in the psychological group ($P < 0.05$).

The comparison of daily living ability between the normal and psychological group

Figure 1C shows that before rehabilitation, there was no difference in the BI scores between the normal and psychological groups ($P > 0.05$). After 1, 2, and 3 wk of rehabilitation, the BI score improved in both groups ($P < 0.05$), and the BI score in the normal group was higher than that in the psychological group ($P < 0.05$).

The correlation between negative emotions and limb rehabilitation

As shown in Table 2, there was a negative correlation between anxiety and upper, lower limb FMA scores at 1-, 2- and 3-wk post rehabilitation ($P < 0.05$). There was a negative correlation between depression and upper, lower limb FMA scores at 1-, 2- and 3-wk post rehabilitation ($P < 0.05$). These results suggested a negative correlation between negative emotions and limb rehabilitation.

The correlation between negative emotions and daily living ability

There was a negative correlation between anxiety and BI scores at 2- and 3-wk post rehabilitation ($P < 0.05$), and there was a negative correlation between depression and BI scores at 1-, 2- and 3-wk post rehabilitation ($P < 0.05$) (Table 3). These results suggest a negative correlation between negative emotions and activities of daily living.

Table 1 The comparison of general data between normal and psychological groups

Index	Normal group (n = 40)	Psychological group (n = 40)	t/χ^2	P value
Gender (male, %)	24 (60%)	25 (62.5%)	-0.053	0.818
Age (yr)	65.33 ± 4.59	65.90 ± 4.91	-0.541	0.590
BMI (kg/m^2)	25.43 ± 2.08	25.86 ± 1.74	-0.997	0.322
Course of disease (d)	27.93 ± 7.11	27.83 ± 7.88	0.060	0.953

BMI: Body mass index.

Table 2 The correlation between emotions and limb rehabilitation

	FMA score of upper limb			FMA score of lower limb		
	1 wk	2 wk	3 wk	1 wk	2 wk	3 wk
Anxiety	r = -0.341	r = -0.339	r = -0.592	r = -0.288	r = -0.289	r = -0.454
	P = 0.005	P = 0.002	P < 0.001	P = 0.010	P = 0.009	P < 0.001
Depression	r = -0.319	r = -0.233	r = -0.585	r = -0.369	r = -0.255	r = -0.475
	P = 0.012	P = 0.038	P < 0.001	P = 0.001	P = 0.023	P < 0.001

FMA: Fugl-Meyer assessment.

Table 3 The correlation between emotions and daily living ability

	BI score		
	1 wk	2 wk	3 wk
Anxiety	r = -0.199	r = -0.377	r = -0.395
	P = 0.077	P = 0.001	P < 0.001
Depression	r = -0.233	r = -0.379	r = -0.387
	P = 0.038	P = 0.001	P < 0.001

BI: Barthel index.

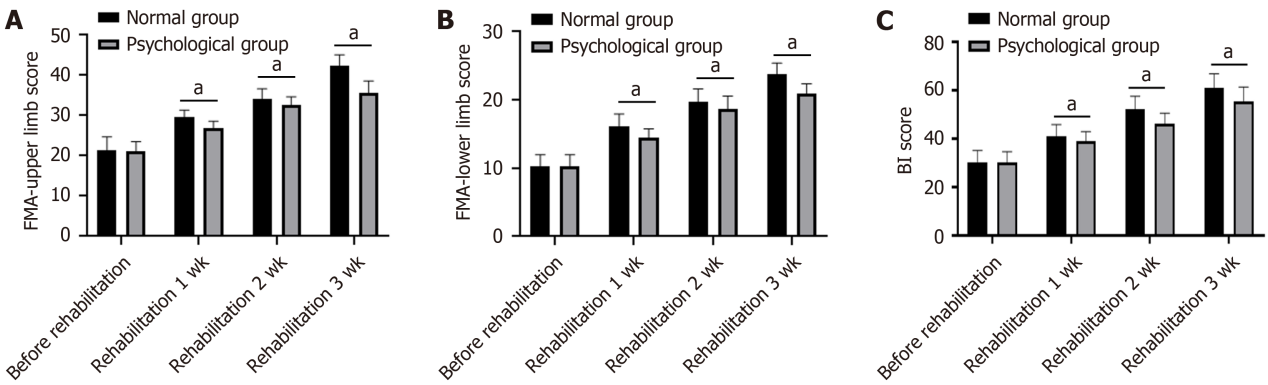

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Figure 1 The comparison of motor function and daily living ability between normal and psychological groups. A: Fugl-Meyer assessment (FMA)-upper limb score; B: FMA-lower limb score; C: Daily living ability. FMA: Fugl-Meyer assessment. BI: Barthel index. ^aP < 0.05.

DISCUSSION

The incidence of cerebrovascular diseases and stroke, which is the most common type of cerebrovascular disease[15], has increased annually, and they generally occur in the younger and middle-aged group[16]. Once affected by stroke, patients with mild disease may experience delayed movement, whereas those with severe disease phenotypes may experience limb dysfunction and even death. Some people may experience a series of changes in their psychological state after illness, which affects rehabilitation training and recovery of limb function[17]. Elderly people have decreased bodily functions, more comorbidities, and a strong psychological dependence on their families[18]. After a period of illness, they not only have to endure the torment of illness but also the inconveniences of life. These patients bear significant psychological pressure as a result.

Many patients find it difficult to complete role conversion in a short time; the rehabilitation training initiative is poor, the effect is not obvious, depression and pessimism appear, psychological resilience becomes affected, and it is easily complicated with acute stress disorder; that is, some separation symptoms, such as mental, movement, and personality dysfunction appear in the early stages of the illness[19]. Those with avoidance and high vigilance towards illness events deliberately avoid the facts about one's own illness, suspect the gaze of others, are unable to control one's emotions and temper, and are prone to irritability, anger, and poor sleep quality[20].

This study used the HADS to evaluate the psychological status of patients with limb movement disorders after stroke and to determine whether they had anxiety and depression before rehabilitation initiation. In previous studies that followed-up stroke patients, it was hypothesized that fear of pain affects post-stroke functional recovery; however, there was no correlation between the two[21]. It is recommended that patients pay attention to their fears and receive reasonable psychological interventions. Related studies suggest that anxiety and depression affect the recovery of limb function in stroke patients[22]. Our study showed that the motor function and daily living ability of stroke patients in the psychological group were lower than those in the normal group after 1-, 2-, and 3-wk of rehabilitation, indicating that anxiety and depression negatively impact the recovery of motor function and daily living ability. Further, our research showed a significant negative correlation between negative emotions such as anxiety and depression, motor function, and self-life ability. This was because patients in the psychological group had a poor psychological state and lacked the ability to withstand stress[23]. They are unable to establish a good buffer time after the illness, which is not conducive to the creation of positive emotions and is even less conducive to the recovery of upper and lower limb function after stroke[24].

Therefore, we should attach importance to the psychological state of patients before rehabilitation, and it is recommended that future studies address the following points to achieve better outcomes: Firstly, rehabilitation plans should be developed to improve patients' quality of life, take effective psychological intervention measures, and observe and evaluate the actual effects. This may be done by equipping dedicated psychologists with the correct resources to strengthen research on the psychological status of stroke patients before rehabilitation. Secondly, optimal treatment methods should be adopted to reduce and eliminate the adverse effects of psychological factors on limb motor function before rehabilitation. Furthermore, attention should be paid to the psychological rehabilitation of patients after discharge and to strengthen follow-up procedures. Finally, the active cooperation between psychologists and rehabilitation physicians must be strengthened to minimize negative psychological impacts.

Our study has several limitations. There are many factors that affect the recovery of limb motor function, and psychological factors are only one of them. This study only considered the effects of anxiety and depression on limb motor function recovery before rehabilitation. Further research is needed to investigate the effects of other factors on recovery of limb motor function. The evaluation of various indices in this study are mostly in the form of a subjective numeric rating scale. At the same time, due to differences in language expression and understanding among ethnic minorities, there may have been errors in the measurement of each indicator. In the future, more objective indicators such as imaging findings should be used to quantify the results more accurately. This study only examined the impact of psychological factors before rehabilitation on limb motor function rehabilitation, without considering the impact of psychological factors, and it did not consider effective psychological intervention measures for adverse psychological outcomes. This must be investigated in the future. Finally, sample size of this study was small, and future multi-center studies with larger sample sizes are needed to confirm this finding.

CONCLUSION

In summary, there is a certain correlation between the psychological state of patients with limb disorders after stroke and their level of limb rehabilitation; the greater the negative emotions, the worse the rehabilitation effect. In clinical practice, healthcare workers can assist in the rehabilitation of patients' limb functions by improving their psychological state, indirectly improving their quality of life.

ARTICLE HIGHLIGHTS

Research background

The rehabilitation of limb function in patients with limb movement disorders after stroke is influenced by their psychological state.

Research motivation
Exploring whether healthcare workers can accelerate the recovery of limb function in stroke patients by improving their psychological state and indirectly improving their quality of life.

Research objectives
The aim of this study was to investigate the correlation between the level of motor rehabilitation and the psychological state of patients with limb movement disorders post stroke.

Research methods
Eighty patients with limb dysfunction after stroke were retrospectively selected. The Fugl-Meyer assessment motor function and Barthel index daily living ability scales were used to investigate limb movement disorders and daily living ability, and a correlation between the two indices and psychological state was observed.

Research results
There was a negative correlation between negative emotions and limb rehabilitation and between negative emotions and daily living ability.

Research conclusions
The better the psychological state of patients with limb movement disorders after stroke, the more significant the rehabilitation effect on limb function recovery.

Research perspectives
When performing limb function rehabilitation in patients with limb movement disorders after stroke, it is necessary to pay attention to the patient's psychological state. A good psychological state can accelerate recovery.

FOOTNOTES

Author contributions: Li XW designed the study and wrote the paper; Fu QZ designed the study and supervised the report; Xin YF organized and analyzed the data; Zhang XG and Weng Y provided clinical advice; Chang AH and Yang JH organized the references.

Institutional review board statement: The study was reviewed and approved by the First Affiliated Hospital of Henan University of Science and Technology (Approval No. 2022-03-B160).

Informed consent statement: This study used only anonymous patient data and exempted the requirement for informed consent according to policy.

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ORIGINAL ARTICLE

Observational Study

Relationship between primary caregivers' social support function, anxiety, and depression after interventional therapy for acute myocardial infarction patients

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Abstract

BACKGROUND

An acute myocardial infarction (AMI) is often treated with direct coronary intervention and requires home-based rehabilitation. Caregivers of patients with AMI need adequate social support to maintain high-quality care; however, their social support function is low, and relevant indicators for intervention must be identified.

AIM

To analyze the correlation between social support for primary caregivers, their anxiety, and depression, when caring for patients with AMI after interventional therapy.

METHODS

Using convenience sampling, we selected 300 primary caregivers of patients with AMI who had undergone interventional therapy. The Social Support Rating Scale (SSRS), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS) were used to assess the primary caregivers. A Pearson's correlation analysis was used to analyze the correlations between the SSRS, SAS, and SDS, and a multiple logistic regression analysis was used to analyze the factors influencing the low social support function of primary caregivers. The receiver operating characteristic curve and area under the curve (AUC) were used to evaluate the predictive ability of the SAS and SDS for low social support function in primary caregivers.

RESULTS

Considering the norm among Chinese people, AMI caregivers' objective support, subjective support, support utilization, and SSRS scores were lower, while their SAS and SDS scores were higher. The SSRS scores of female caregivers were higher than those of the male caregivers (t = 2.123, P = 0.035). The Pearson correlation analysis showed that objective support, subjective support, support utilization, and SSRS total scores were significantly correlated with both SAS (r = -0.414, -0.460, -0.416, -0.535) and SDS scores (r = -0.463, -0.379, -0.349, -0.472). Among the 300 AMI caregivers, 56 cases (18.67%) had a low level of support function (SSRS ≤ 22 points). Logistic regression model analysis showed that SAS and SDS were independent risk factors for low social support function of AMI caregivers, regardless of adjustment for other variables (P < 0.05). SAS and SDS predicted that the AUC of AMI caregivers with low support function was 0.84, sensitivity was 67.9 and 71.4, and specificity was 84.0 and 70.9, respectively.

CONCLUSION

The social support function of the primary caregiver of patients with AMI after interventional therapy was lower and negatively correlated with anxiety and depression in the primary caregiver.

Key Words: Acute myocardial infarction; Primary caregivers; Social support function; Anxiety; Depression; Relationship

Core Tip: High levels of social support help caregivers implement care. Intervention in the social support function of the primary caregiver is beneficial for the postoperative recovery of patients with acute myocardial infarction (AMI) after interventional therapy. To find a new intervention direction, we proposed a relationship between the social support function of primary caregivers of patients with AMI, and anxiety and depression; this is a breakthrough in improving the social support function of primary caregivers.

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INTRODUCTION

Acute myocardial infarction (AMI) is myocardial necrosis caused by acute or persistent ischemia and hypoxia in the coronary arteries. It is typically characterized by persistent chest pain[1]. Usually, after rest and use of nitrates, patients do not receive complete relief but experience arrhythmia, shock, or heart failure, resulting in loss of daily living ability and serious mental and behavioral disorders. According to relevant surveys and research data, the incidence of AMI in China has increased sharply in recent years, with the average annual number of new cases exceeding 500000[2]. Acute ST-elevation myocardial infarction (STEMI) within 12 h is usually treated with direct coronary intervention[3]. Postoperatively, most patients require home-based rehabilitation and caregiver care. During rehabilitation, the physical and mental state of the caregiver affects the prognosis and degree of recovery of the patient. The patient's condition also affects the physical and psychological states, as well as the quality of the caregiver's life, thus affecting their ability and quality of care[4]. Caregivers experience physical and emotional stress during the long-term care process. As a relative of the patient, the caregiver experiences heavy emotional stress and shoulders financial pressure. Studies have found that if caregivers receive sufficient social support, they can maintain their physical and mental health better and adapt to their caregiving role[5]. Ensuring a high social support function for caregivers has a positive clinical significance for patients' rehabilitation. However, there is a lack of effective intervention strategies to improve caregivers' social support, and more clinical evidence is needed to support the factors related to social support. Research has found that caregivers of patients with AMI often have different negative emotional levels of anxiety and depression[6,7]. Therefore, we propose that the social support function of caregivers of patients with AMI may be related to anxiety and depression. Based on this, we selected 300 primary caregivers of patients undergoing interventional treatment for AMI.

Considering the above, this study aims to investigate the levels of social support, anxiety, and depression among caregivers of AMI patients, and analyze the correlation between the social support function of main caregivers and their anxiety and depression after interventional therapy, to provide a reference for improving the quality of home care.

MATERIALS AND METHODS

Source of research object

Using convenience sampling, we selected 300 primary caregivers of patients with AMI who received concurrent interventional treatment at the Affiliated Hospital of Jiangnan University, between January 2021 and December 2022.

Patients needed to comply with the following conditions: (1) Show AMI symptoms and evidence of myocardial ischemia[8]; (2) Be diagnosed with acute STEMI within 12 h and treated with coronary intervention; and (3) Be 18 years or older. The caregiver was required to meet the following conditions: (1) Be at least 18 years of age; (2) Be the patient's immediate family member and has been caring for the patient for the longest time (*i.e.*, is the patient's primary caregiver); (3) Have normal reading and writing ability and be able to complete the questionnaire independently; and (4) Be aware of this research and voluntarily agree to be investigated. The caregiver could not have the following conditions: (1) Mental abnormalities or intellectual disabilities; (2) Language expression and communication barriers; (3) A history of alcohol or drug dependence; or (4) Be a paid caregiver.

Survey tool

General information questionnaire. Based on a literature review and expert consultation, a general information questionnaire was prepared, which included age, gender, number of hospitalizations, payment method of medical expenses, proportion of out-of-pocket medical expenses to family income, course of the disease, heart function, and daily living ability. Caregivers' general information included age, gender, education level, marital status, relationship with patients, monthly family income, caretaking experience, number of other caregivers, *etc.*, as well as the age of patients, time from onset to admission, and Killip grade.

The Social Support Rating Scale (SSRS)[9] was created by domestic scholar Xiao Shui-Yuan in 1986, to assess the status of people's social support, including subjective support, objective support, and support utilization. The scale comprises three dimensions and ten items, with the total score being the sum of the scores for each item. Higher scores indicate higher levels of social support. The total score is 66 points, of which ≤ 22 points are rated as low level, 23–44 points as medium, and 45–66 points as high. The retest reliability is 0.92, and the reliability and validity of all items are high (Cronbach's α coefficient was 0.89–0.94). The SSRS Chinese norm refers to the work of Zhang *et al*[10], in which a norm established based on the population of the whole country as a sampling population. This is the reference value.

The Self-Rating Anxiety Scale (SAS)[11], developed by Zung in 1971, was used to assess the subjective feelings of patients with anxiety. The scale contains 20 items and the score criteria are as follows: 1 point for no or very little time; 2 points for a small amount of time; 3 points for more time; and 4 points for most of the time. The scores were added together to obtain a rough score, and multiplied by 1.25 to obtain a standard score. The higher the score, the greater the anxiety. The Cronbach's α coefficient of the scale was 0.931.

The Self-Rating Depression Scale (SDS)[12] developed by Zung in 1965 was used to assess the subjective feelings of patients with depression, with a total of 20 items. The scoring criteria for each item were as follows: Occasionally, 1 point; sometimes, 2 points; often, 3 points; and always, 4 points. The total score is rough, and the gross score multiplied by 1.25 equals the standard score. Higher scores indicate more severe depression. The Cronbach's α coefficient of the scale was 0.927. Both SAS and SDS Chinese norms refer to the literature of Kang[13], which provides a norm based on the population of the whole country as a sampling population, and has reference value.

Investigation method

Community doctors or nurses with uniform training conducted household surveys with primary caregivers or invited them to community health service institutions to complete the surveys. The researcher informed the primary caregivers of the purpose, significance, and participation method of the survey and encouraged them to provide their informed consent, which was explained to them in simple and understandable language. Subsequently, the primary caregivers completed the questionnaire. The researchers assisted those with low cultural or language abilities in completing the questionnaires. Questionnaires were completed with confidential information and collected immediately. A total of 329 questionnaires were sent out; 306 questionnaires were returned, and 300 effective questionnaires were obtained; an effective rate of 98.04%.

Quality control

To reduce the risk of privacy disclosure, the respondents were surveyed anonymously. We arranged the questionnaire survey in an independent room, allowed the investigator and primary caregiver to be present during the investigation, and entered the data through double cross-entry and cross-examination.

Statistical analysis

SPSS (version 23.0) was used for the data analysis and processing. Case numbers described counting data; mean ± standard deviation describes measurement data tested by a line test or an F-test; a Pearson's correlation was used to analyze correlation, a multiple linear regression explored risk factors, and receiver operator characteristic curve (ROC) and area under the curve (AUC) predicted ability evaluation; Test level: $\alpha = 0.05$.

Table 1 Comparison of Social Support Rating scale scores of primary caregivers with Chinese norms

SSRS items	SSRS score (*n* = 300)	Chinese norm (*n* = 3342)	*t* value	*P* value
Objective support	7.05 ± 1.6	9.1 ± 3.0	11.690	< 0.001
Subjective support	16.9 ± 5.0	23.5 ± 4.3	25.110	< 0.001
Support utilization	4.7 ± 1.3	7.8 ± 2.0	26.350	< 0.001
Total scores of AMI caregivers	28.56 ± 5.31	40.5 ± 2.8	64.230	< 0.001

SSRS: Social Support Rating scale; AMI: Acute Myocardial Infarction.

Table 2 Comparison of Self Rating Anxiety Scale scores and SDS scores of primary caregivers with Chinese norms

Items	Scores (*n* = 300)	Chinese norm (*n* = 1338)	*t* value	*P* value
SAS	41.26 ± 6.58	29.78 ± 10.07	18.860	< 0.001
SDS	44.16 ± 7.54	33.46 ± 8.55	20.000	< 0.001

SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale.

RESULTS

Primary caregivers had low SSRS

Compared with the Chinese norm, the objective support, subjective support, support utilization, and total scores of AMI caregivers were lower ($P < 0.05$) (Table 1).

The SAS and SDS scores of primary caregivers were higher

Compared with the Chinese norm, the scores of SAS and SDS among caregivers of patients with AMI were higher ($P < 0.05$) (Table 2).

SSRS scores of primary caregivers with different characteristics

There were no differences in the SSRS scores among different age groups, gender, education level, marital status, relationship with patients, monthly family income, caregiving experience, number of other caregivers, age of patients, time from onset to admission, or Killip rating of patients ($P > 0.05$); however, the SSRS scores of female caregivers were higher than those of male caregivers ($P < 0.05$) (Table 3).

Correlation between the SSRS score and SAS score or SDS score

Through the Pearson correlation analysis, objective support, subjective support, support utilization, and total SSRS scores were found to be negatively correlated with SAS (r = -0.414, -0.460, -0.416, -0.535, respectively) and SDS scores (r = -0.463, -0.379, -0.349, -0.472, respectively) ($P < 0.05$) (Table 4).

Multiple regression analysis affecting primary caregiver support function

Among the 300 AMI caregivers, 56 cases (18.67%) had a low level of support function (SSRS ≤ 22 points). We used the support function (1 = low level, 0 = medium-high level) as the dependent variable and the characteristic indicators as self-variables (assigned values are shown in Table 5) of the logistic regression model analysis. SAS and SDS were independent determinants of low support function among AMI caregivers, regardless of adjustment for other variables ($P < 0.05$) (Table 6).

The ability of SAS and SDS scores to predict low social support function in AMI caregivers

The AUC of the SAS and SDS for predicting AMI caregivers with low social support function was 0.84, sensitivity was 67.9 and 71.4, and specificity was 84.0 and 70.9, respectively (Table 7 and Figure 1).

DISCUSSION

At present, the mental health outlook of family caregivers of patients with AMI in China is not optimistic, which directly affects their caring ability. The poor caring ability of caregivers not only affects the condition and prognosis of patients with AMI but also affects their physical and mental health. Therefore, it is necessary to explore the relationship between the social support function of primary caregivers, their anxiety, and their depression.

Table 3 Social Support Rating Scale scores of primary caregivers with different characteristics

Characteristics	Cases	SSRS scores	*t/F* value	*P* value
Age			1.317	0.189
< 60 yr	229	29.47 ± 6.96		
≥ 60 yr	71	28.25 ± 6.34		
Gender			2.123	0.035
Female	172	29.47 ± 6.96		
Male	128	27.89 ± 5.49		
Education levels			1.172	0.311
Junior high school and below	83	28.96 ± 7.16		
High school or technical secondary school	100	30.07 ± 6.24		
College or above	117	28.71 ± 6.98		
Marital status			3.382	3.382
Never married	80	28.44 ± 8.03		
Married	153	27.42 ± 5.45		
Divorced or widowed	67	29.84 ± 6.25		
Relationship with patients			0.8741	0.874
Mate	105	27.98 ± 5.67		
Parent	98	27.76 ± 6.70		
Sons and daughters	65	29.09 ± 7.09		
Other	32	29.28 ± 7.11		
Monthly family income			0.607	0.546
< 5000 RMB	96	28.72 ± 6.85		
5000–10000 RMB	128	27.95 ± 5.39		
> 10000 RMB	76	28.79 ± 6.76		
Caregiving experience			0.149	0.882
No	202	29.29 ± 7.46		
Yes	98	29.16 ± 6.30		
Number of other caregivers			1.036	1.036
0	55	29.62 ± 6.15		
1 or 2	157	28.65 ± 7.003		
≥ 3	88	27.95 ± 6.67		
Age of patients			0.571	0.568
< 60 yr	221	28.63 ± 7.42		
≥ 60 yr	79	29.17 ± 6.59		
Time from onset to admission			0.683	0.495
< 10 h	114	29.21 ± 6.64		
≥ 10 h	186	28.64 ± 7.23		
Killip rating of patients			1.065	0.288
Level 1 or 2	221	28.82 ± 7.15		
Level 3 or 4	79	27.84 ± 6.64		

Table 4 Correlation between Social Support Rating Scale score, Self Rating Anxiety Scale score, and Self Rating Depression Scale score

SSRS items	SAS score		SDS score	
	r value	*P* value	*r* value	*P* value
Objective support	-0.414	< 0.001	-0.463	< 0.001
Subjective support	-0.460	< 0.001	-0.379	< 0.001
Support utilization	-0.416	< 0.001	-0.349	< 0.001
Total SSRS score	-0.535	< 0.001	-0.472	< 0.001

SSRS: Social Support Rating Scale; SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale.

Table 5 Assignment

Independent variable	Assignment
Age	0 = < 60 yr, 1 = ≥ 60 yr
Gender	0 = female, 1 = male
Education levels	0 = junior high school and below, 1 = high school or technical secondary school, 2 = college or above
Marital status	0 = spinsterhood, 1 = married, 2 = divorced or widowed
Relationship with patients	0 = mate, 1 = parent, 2 = sons and daughters, 3 = other
Monthly family income	0 = < 5000 RMB, 1 = 5000–10000 RMB, 2 = > 10000 RMB
Caregiving experience	0 = no, 1 = yeas
Number of other caregivers	0 = 0, 1 = 1 or 2, 2 = ≥ 3
Age of patients	0 = < 60 yr, 1 = ≥ 60 yr
Time from onset to admission	0 = < 10 h, 1 = ≥ 10 h
Killip rating of patients	0 = level 1 or 2, 1 = level 3 or 2

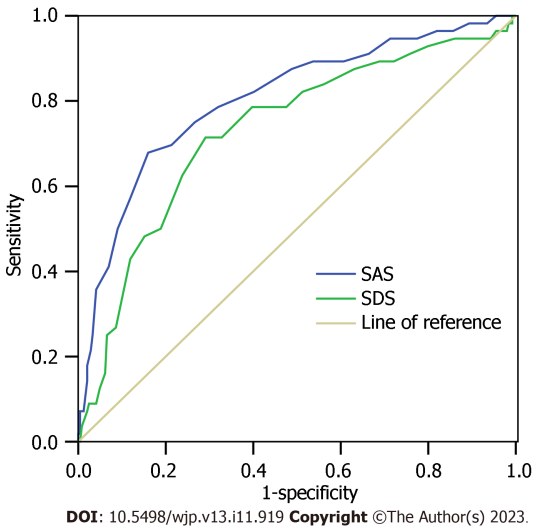

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Figure 1 Receiver operator characteristic curve analysis of Self-Rating Anxiety Scale score and Self-Rating Depression Scale score prediction. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.

Table 6 Multiple regression analysis affecting primary caregiver support function

Independent variable	B	SE	Wals	*P* value	OR	95% CI	
						Lower limit	Upper limit
No other variables were adjusted							
SAS	0.177	0.032	30.813	< 0.001	1.194	1.121	1.271
SDS	0.070	0.026	7.288	0.007	1.072	1.019	1.128
Constant	-12.392	1.723	51.741	< 0.001	< 0.001		
After adjusting for other variables							
SAS	0.193	0.035	30.566	< 0.001	1.213	1.133	1.300
SDS	0.068	0.028	6.008	0.014	1.071	1.014	1.131
Age	-0.261	0.488	0.287	0.592	0.770	0.296	2.003
Gender	0.133	0.395	0.113	0.737	1.142	0.527	2.477
Education levels			0.550	0.760			
High school or technical secondary school	0.298	0.452	0.434	0.510	1.347	0.555	3.269
College or above	-0.044	0.449	0.010	0.922	0.957	0.397	2.306
Marital status			0.140	0.932			
Married	0.091	0.535	0.029	0.864	1.096	0.384	3.127
Divorced or widowed	-0.073	0.462	0.025	0.875	0.930	0.376	2.298
Relationship with patients			1.974	0.578			
Parent	0.253	0.694	0.133	0.715	1.288	0.331	5.019
Sons and daughters	0.759	0.699	1.179	0.278	2.135	0.543	8.400
Other	0.339	0.728	0.217	0.641	1.404	0.337	5.848
Monthly family income			3.042	0.218			
5000–10000 RMB	0.453	0.462	0.960	0.327	1.573	0.636	3.893
> 10000 RMB	-0.281	0.519	0.293	0.588	0.755	0.273	2.087
Caregiving experience	-0.294	0.399	0.540	0.462	0.746	0.341	1.631
Number of other caregivers			1.015	0.602			
1 or 2	0.351	0.552	0.406	0.524	1.421	0.482	4.188
≥ 3	0.416	0.418	0.991	0.320	1.515	0.668	3.435
Age of patients	-0.051	0.439	0.013	0.908	0.950	0.402	2.249
Time from onset to admission	-0.008	0.385	0.000	0.983	0.992	0.467	2.108
Killip rating of patients	-0.172	0.424	0.164	0.685	0.842	0.367	1.933
Constant	-13.699	2.070	43.780	< 0.001	< 0.001	–	–

SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale; B: Regression Coefficient β; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval.

Table 7 Self Rating Anxiety Scale scores and Self Rating Depression Scale scores predicted the area under the curve of primary caregivers with low levels of social support

Test result variable	AUC	SE	*P* value	95%CI	Sensitivity (%)	Specificity (%)	Optimum cutoff value
SAS	0.84	0.84	< 0.001	0.737, 0.872	67.9	84.0	45.5
SDS	0.84	0.84	< 0.001	0.655, 0.807	71.4	70.9	47.5

SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale; AUC: Area under the curve; CI: Confidence interval.

The occurrence of AMI affects not only patients, but also their families and caregivers[14]. Compared with the norms in China, caregivers' objective support, subjective support, support utilization, and total SSRS scores were lower, while the SAS and SDS scores were higher. This indicates that the social support function of primary caregivers was generally low, and that negative emotions of anxiety and depression were more common, which should be considered. These results confirm those of previous studies[15,16]. The social support function of primary caregivers was generally low, which may be due to an imperfect medical security system and deficiencies in follow-up and community nursing, resulting in less social support for primary caregivers. Additionally, problems such as drug side effects and social discrimination can indirectly lead to primary caregivers' self-isolation and reluctance to seek outside help, thereby greatly reducing the availability of social support. Good social support stems from the need for spiritual comfort and support from family, friends, and community. This situation serves as a warning to medical staff to pay attention to social support, assist primary caregivers in establishing social support systems, and enhance their social support functions.

Anxiety is defined as an inner restlessness and fear with no obvious objective causes, whereas depression is defined as persistent low mood in terms of clinical characteristics of the state of mind. The long-term care of patients with AMI undergoing interventional surgery negatively affects the mental health of their primary caregivers. Because AMI is often associated with varying degrees of dysfunction after surgery, the primary caregiver must provide frequent in-bed turning and back-patting to prevent bedsores and transfer patients between beds and wheelchairs. The primary caregiver takes care of the patient in various aspects, such as daily activities, daily living, and diet, and expends a lot of physical strength, time, and energy, which is extremely costly for the body and mind of the primary caregiver and must be maintained for a long time. Primary caregivers also face personality changes in patients with AMI, which will produce psychological reactions such as helplessness, depression, anger, loneliness, and boredom during the care process, affecting normal emotional functions. Patients who have not fully recovered after surgery may relapse[17]; moreover, their primary caregivers must consider both the patient's condition and the financial burden it brings. Such repeated worries aggravate anxiety and depression.

Social support refers to the help people receive from society or others through their social networks; it includes objective support, subjective support, and support utilization. According to the results of our Pearson's correlation analysis, objective support, subjective support, support utilization, and total SSRS scores were significantly negatively correlated with SAS and SDS scores, suggesting that with the increase in anxiety and depression among primary caregivers of patients with AMI, their social support function is lower, which is consistent with some existing research results[18,19]. Further, our multiple linear regression analysis found that the SAS score [odds ratio (OR) = 1.194] and SDS score (OR = 1.072) were independent influencing factors of low social support function in primary caregivers; these two indicators could accurately predict the risk of low social support, and the sensitivity and specificity of the prediction reached more than 65%. The results showed that, after excluding other interfering factors, the lower the anxiety and depression experienced by the primary caregiver, the stronger the social support function. A possible explanation for this effect is that the lower the social support function of the primary caregiver, the greater the caring burden[20], and the more likely it is to produce anxiety and depression. Research also shows that good social support can not only promote the physical health of caregivers, but also effectively relieve their depression and anxiety[13]. According to research by the Chinese Academy of Social Sciences, social support can not only improve the psychological satisfaction of the body, but also alleviate its negative emotions[21]. Therefore, the community should not only pay attention to the primary caregivers of AMI patients undergoing interventional surgery, but should also strengthen the care and help of caregivers by providing adequate psychological support and encouragement. Family visits, caregiver experience exchange platforms, rehabilitation guidance, and other measures can reduce the burden on caregivers, improve the mental health of caregivers and patients, and achieve a win–win outcome.

The limitations of this study is that it is a single-center study, and the results can only reflect part of the population; therefore, whether it can be generalized to the general population is unknown. Further, the inclusion of characteristic indicators of primary caregivers is limited, meaning that potential impact indicators may have been overlooked. Therefore, future studies should include multi-center data and add characteristic indicators to enhance the reliability of the results of this study.

CONCLUSION

The social support function of the primary caregiver of patients with AMI after interventional therapy was low and negatively correlated with anxiety and depression of the primary caregiver. For primary caregivers with anxiety and depression, timely attention and providing a deep examination of underlying issues should be provided to reduce adverse emotional distress, so that the caregiver can maintain a happy mood and implement care.

ARTICLE HIGHLIGHTS

Research background

After interventional therapy, most patients need care at home, from their caregivers. The social support function of primary caregivers is an important factor affecting the quality of care and prognosis of patients. Primary caregivers often experience varying degrees of anxiety and depression.

Research motivation

It is necessary to understand the correlation indicators of primary caregivers' social support functions to better guide clinical interventions. Considering that primary caregivers tend to have different levels of anxiety and depression, we speculate that their social support function may be related to anxiety and depression.

Research objectives

To explore the relationship between anxiety, depression, and the social support function of primary caregivers of patients with acute myocardial infarction (AMI) undergoing interventional surgery.

Research methods

Investigate the primary caregivers of AMI patients undergoing interventional surgery using the Social Support Rating Scale (SSRS), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS). The correlation between the SSRS and SAS or SDS was evaluated using a Pearson's correlation analysis, multiple linear regression, receiver operator characteristic curve (ROC), and area under the curve (AUC).

Research results

The SSRS was negatively correlated with the SAS and SDS scores. SAS and SDS were independent factors for low SSRS and could predict the risk of low SSRS.

Research conclusions

The social support function of primary caregivers of AMI patients undergoing interventional surgery is associated with anxiety and depression.

Research perspectives

Based on the Pearson's correlation analysis, multiple linear regression, ROC, and AUC, we comprehensively analyzed the correlation between the SSRS, SAS, and SDS scores of primary caregivers of patients with AMI who underwent interventional surgery, confirming that the social support function of primary caregivers is closely related to anxiety and depression, which is instructive for clinical intervention.

FOOTNOTES

Author contributions: Bao J designed the research and wrote the paper; Zou LT supervised the report; Wang XY contributed to the analysis; and Chen CH provided clinical advice.

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ORIGINAL ARTICLE

Observational Study

Depression and sarcopenia-related traits: A Mendelian randomization study

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Abstract

BACKGROUND

Observational studies have suggested that depression is associated with sarcopenia. However, the causal relationship between depression and sarcopenia remains unclear.

AIM

To investigate the causal relationship between depression and sarcopenia.

METHODS

We performed a Mendelian randomization (MR) analysis to identify the bidirectional relationship between depression and sarcopenia-related traits. Summary-level data and independent variants used as instrumental variables came from large genome-wide association studies of depression (414055 cases and 892299 controls), of appendicular lean mass (ALM, 450243 participants), and of hand grip strength (exposure: 360000 participants; outcome: 334925 participants).

RESULTS

We identified a negative association of depression with lower ALM [odds ratio (OR): 0.932, 95% confidence interval (95%CI): 0.889-0.979, $P = 0.005$]. In the reverse MR analysis, we also observed an inverse association of hand grip strength with depression (OR: 0.200, 95%CI: 0.108-0.370, $P < 0.001$). Similar results were obtained in sensitivity analyses.

CONCLUSION

Depression was causally related to decreased muscle mass, and declined muscle strength might lead to a higher risk of depression.

Key Words: Appendicular lean mass; Depression; Hand grip strength; Mendelian randomization; Older adults; Sarcopenia

Core Tip: In this Mendelian randomization study, we established a bidirectional relationship between depression and reduced muscle mass, specifically lower appendicular lean mass and hand grip strength. Our findings highlight a potential bidirectional relationship between depression and sarcopenia with implications for both mental and physical health.

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INTRODUCTION

Sarcopenia is a complex geriatric disorder marked by a gradual and progressive reduction of skeletal muscle mass, decrease in skeletal muscle strength, and deterioration in physical performance[1]. In addition to elevating the risks of disability, sarcopenia also relates closely to a wide range of adverse consequences, such as falls, hospitalization due to fall-related injuries, and even mortality[2,3]. As the population ages, the prevalence of sarcopenia increases, making it an important public health issue and a global health burden. In addition, depression is common among the elderly, with an average 12-mo occurrence rate of approximately 6%. This is related to negative health consequences, including increased mortality and reduced quality of life[4,5]. Thus, depression and sarcopenia are important concerns for the elderly population, and it is crucial to establish a clear understanding of their relationship.

Numerous observational studies have suggested that depression and sarcopenia are common comorbidities, but there is no direct evidence of causality[6-8]. In a clinical trial investigating sarcopenia as a therapeutic target, the management of sarcopenia was found to be associated with a notable reduction in depressive symptoms[9]. Some studies have suggested that skeletal muscle may influence psychiatric illnesses through neurotrophic factors[10]. However, those studies were unable to provide convincing evidence to elucidate a null association for the effect of depression on sarcopenia.

Mendelian randomization (MR) represents a compelling genetic epidemiological approach that utilizes genetic variants associated with exposures, which can effectively avoid the potential methodological limitations of observational studies, including reverse causation bias. We conducted this bidirectional MR study to examine the causal relationship between depression and sarcopenia.

MATERIALS AND METHODS

Study design

The diagram of this MR study is displayed in the Figure 1. The genetic variations selected as instrumental variables (IVs) were based on three predominant assumptions: (1) Selected IVs are strongly associated with exposures; (2) There is no observed association between the IVs and potential confounding factors; and (3) The IVs affect outcomes only through exposures without any other pathways[11].

IVs

The IVs for the MR analyses were derived from several different genome-wide association studies (GWASs). Single nucleotide polymorphisms (SNPs) were chosen as IVs when the SNPs for exposures reached genome-wide significance ($P < 5.0 \times 10^{-8}$). All IVs were clumped for independence (linkage disequilibrium $r^2 < 0.1$; region size, 3000 kb) according to the European data from the 1000 Genomes Project. If the SNPs for exposures were not available in the outcome datasets, proxy SNPs (linkage disequilibrium $r^2 > 0.8$) were adopted online (ldlink.nci.nih.gov/). Palindromic SNPs were excluded in the analyses when harmonizing the directions of SNP effects on exposures and outcomes. We also calculated the F-statistics to assess the instrument strength. IVs with F-statistics < 10 were considered to have a weak instrument bias.

Data sources

Genetic IVs associated with depression were obtained from a GWAS meta-analysis that included 414055 cases and 892299 controls from the UK Biobank, 23andMe_307k, and PGC_139k[12]. In the UK Biobank cohort, the depression phenotype, referred to as "broad depression," was determined based on self-reported responses to a web-based questionnaire. In the cohort from 23andMe_307k, the depression phenotype was determined based on self-reported information regarding clinical diagnosis or treatment for depression. In PGC_139k, the depression phenotype was clinically diagnosed. In total, this GWAS identified 102 independent SNPs located at 101 Loci that were associated with depression at a level of

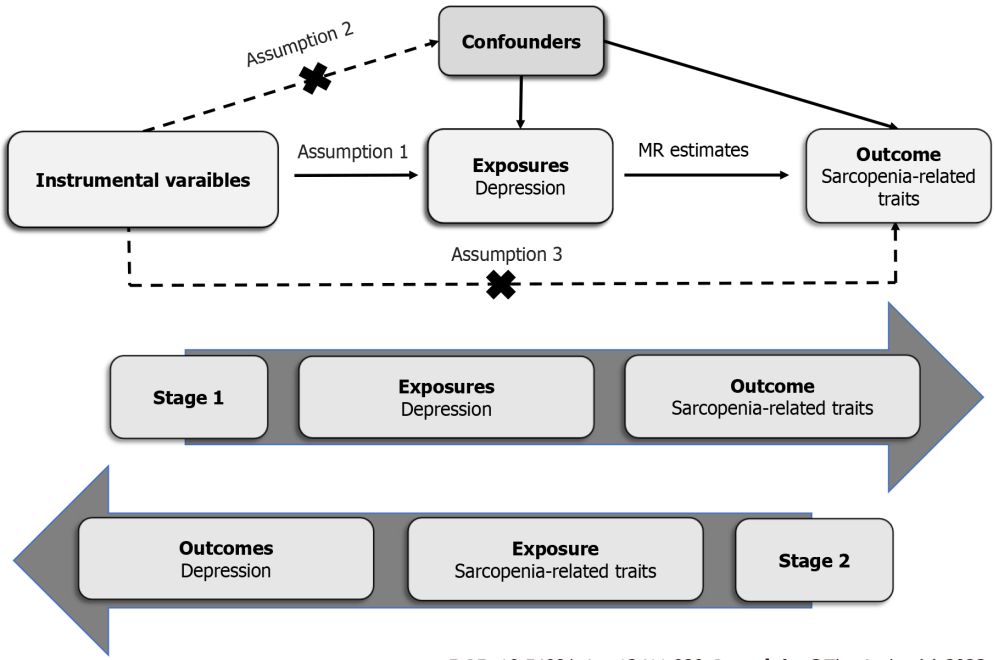

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Figure 1 Principles of the Mendelian randomization study for depression and sarcopenia-related traits. MR: Mendelian randomization.

genome-wide significance, which led to an 8.9% variance in depression.

Appendicular lean mass (ALM) and hand grip strength were selected as a measure of muscle mass and strength. Unlike whole body lean mass, ALM is primarily affected by skeletal muscle and is recommended by the European Working Group on Sarcopenia in Older People due to its high predictive power for sarcopenia-related health outcomes [1]. The summary statistic for ALM was obtained from a GWAS of the UK Biobank (n = 450243)[13]. That GWAS had measured ALM by bioelectrical impedance analysis (BIA) for fat-free mass at the arms and legs. The summary statistic for hand grip strength was obtained from the UK Biobank (nealelab.is/uk-biobank) and included approximately 360000 participants from Europe. Right-hand grip strength (n = 359729) and left-hand grip strength (n = 359704) were meticulously assessed using a calibrated Jamar J00105 hydraulic hand dynamometer adjusted to accommodate hand size variations. We derived 139 independent genetic IVs associated with hand grip from a GWAS from the UK Biobank, which included 334925 individuals[14]. These variants accounted for 1.7% of the variability in grip strength. In this study, relative grip strength was applied, as it may show a better correlation with physical capability than absolute hand grip strength.

Each study incorporated in the GWAS used in the present study was approved by local research ethics committees or Institutional Review Boards, and all participants had given their informed consent.

Statistical analysis

In the main analyses, the random-effects inverse-variance weighted (IVW) approach was applied to evaluate a bidirectional relationship between depression and sarcopenia-related traits[15]. In addition, several sensitivity analyses were also conducted to identify potential pleiotropy. Cochran's Q test was used to assess the heterogeneity among various IVs. The weighted median method was used to include only valid IVs, allowing less than 50% of the genetic variants to be invalid IVs[16]. The MR-Egger method was conducted to detect and correct for any pleiotropic bias[17]. Furthermore, we used the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method to conduct a global test of heterogeneity and to identify horizontal pleiotropy. Any identified SNPs with pleiotropic effects were excluded, and a repeated IVW analysis was subsequently performed to ensure the robustness of the results[18].

All tests were two-sided, and the Bonferroni-corrected significance threshold was set to $P \leq 0.01$ (correcting for 5 outcomes) to account for multiple comparisons. The P values ranging from 0.05 to 0.01 were considered to be suggestive of a potential association between exposures and outcomes. All analyses were conducted using TwoSampleMR and MR-PRESSO packages in R software (Version 4.1.3).

RESULTS

The main characteristics of all SNPs adopted in the MR analyses are shown in Table 1. The F-statistics for all IVs were higher than the threshold of 10, indicating the absence of weak instrument bias in the present study. The summary information of SNPs for the three traits is displayed in Supplementary Tables 1 and 2. The results of Cochran's Q tests and MR-Egger regression are shown in Table 2.

Table 1 Studies and datasets adopted in the Mendelian randomization analyses

Trait	Data source	Sample size, cases/controls	Ancestry
Depression	UK Biobank[1]	127552/233763	European
	23andMe_307K[2]	75607/231747	
	PGC_139K[3]	43204/95680	
	Replication	474574/1032579	
Appendicular lean mass	UK Biobank[1]	450243	European
Hand grip strength, exposures	UK Biobank[1]	Approximately 360000	European
Hand grip strength, outcomes	UK Biobank[1]	334925	European

[1]UK biobank: (1) The broad definition of depression was used in the UK Biobank. Measured in a variety of ways, as follows: Have you ever seen a general practitioner for nerves, anxiety, tension or depression? and have you ever seen a psychiatrist for nerves, anxiety, tension or depression? and (2) Does not include the participants who were identified with bipolar disorder, schizophrenia, or personality disorder using self-declared data as well as prescriptions for antipsychotic medications.
[2]23andMe_307k: (1) The data were derived from the genome-wide association study results from the 23andMe Interactive Discovery projects; and (2) Depression was defined based on responses to web-based surveys, with individuals that self- reported as having received a clinical diagnosis or treatment for depression classified as cases.
[3]PGC_139k: (1) The PGC_139k cohort was obtained from the meta-analysis of major depressive disorder utilizing European-ancestry PGC cohorts with the 23andMe_307k and the previous UK Biobank cohorts removed; and (2) Depression was defined based on structured diagnostic interviews, or electronic medical records, with individuals that self-reported as having received a clinical diagnosis or treatment for depression.

Table 2 Results of potential pleiotropy and heterogeneity assessments in the bidirectional analyses

Parameter	Cochran's Q	*P* for Cochran's Q	Intercept	*P* for intercept
Outcome				
Appendicular lean mass	911.568	< 0.001	-0.002	0.602
Left hand grip strength	409.92	0.004	0.002	0.486
Right hand grip strength	379.511	< 0.001	0.002	0.243
Exposure				
Appendicular lean mass	1401.776	< 0.001	0.001	0.953
Hand grip strength	306.463	< 0.001	0.003	0.887

In the random-effect IVW estimates, genetically determined depression was causally associated with lower ALM [odds ratio (OR): 0.932, 95% confidence interval (95%CI): 0.889–0.979, $P = 0.005$; Figure 2]. This association was robust in the weighted median. The MR-PRESSO analysis identified 18 potential SNP outliers. After removing the outliers, the result was similar. There was significant association of depression with left hand grip and right hand grip (OR: 0.962, 95%CI: 0.936–0.989, $P = 0.007$; OR: 0.961, 95%CI: 0.935–0.987, $P = 0.004$). However, these results were not confirmed in the sensitivity analyses. Several potential SNP outliers were identified in the MR-PRESSO tests. After removing the outliers, the results remained significant.

A significant association was observed between decreased ALM and depression (OR: 0.969, 95%CI: 0.947–0.992, $P = 0.047$; Figure 3). In the sensitivity analyses, weighted median and MR-Egger tests revealed similar effects but with broader confidence intervals. Nine SNPs were detected in the MR-PRESSO test. After removing outliers, the result indicated a suggestive association (OR: 0.978, 95%CI: 0.957–0.999, $P = 0.044$). In addition, genetically determined hand grip strength was causally associated with depression by the IVW method (OR: 0.200, 95%CI: 0.108–0.370, $P < 0.001$). The weighted median method yielded similar results despite the MR-Egger test revealing a null association. In the MR-PRESSO test, three outliers were identified and removed, and the result remained significant.

DISCUSSION

We performed this MR study to explore the bidirectional causal association between depression and sarcopenia. In the forward MR analyses, depression was associated with decreased ALM. Results from IVW suggested that decreased ALM was associated with depression and that depression was associated with lower hand grip strength. However, these results could not be repeated in sensitivity analyses. In the reverse MR analyses, lower hand grip strength was associated with a higher risk of depression. Overall, we reported a significant bidirectional association between depression and

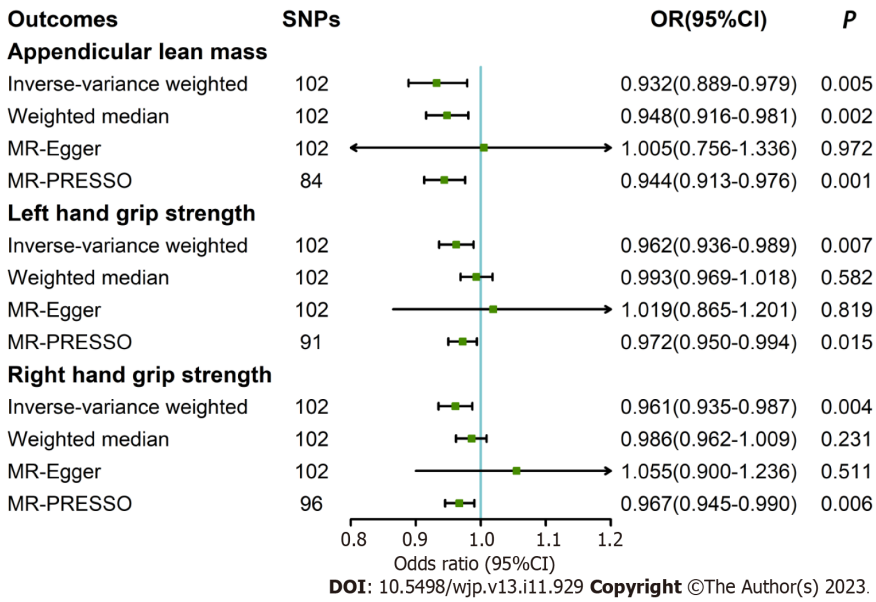

Figure 2 Effect of depression on sarcopenia-related traits. 95%CI: 95%confidence interval; OR: Odds ratio; PRESSO: Pleiotropy Residual Sum and Outlier; SNPs: Single nucleotide polymorphisms.

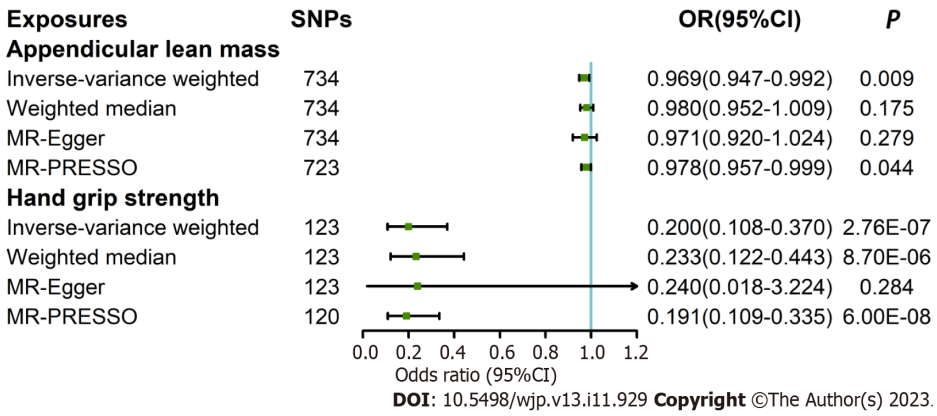

Figure 3 Effect of sarcopenia-related traits on depression. 95%CI: 95%confidence interval; OR: Odds ratio; PRESSO: Pleiotropy Residual Sum and Outlier; SNPs: Single nucleotide polymorphisms.

sarcopenia.

Previous observational studies, mainly cross-sectional in design, suggested that there was a positive association between depression and sarcopenia[8,19-22]. Two meta-analyses included also drew the conclusion that the prevalence of depression in patients with sarcopenia is higher than in the general population[6,7]. Despite considering many common covariates, these studies were still unable to provide evidence of causality between the two conditions. A recent longitudinal study comprising 115601 older adults reported that higher hand grip strength was associated with a lower risk of depression among older adults[23]. Similar results were also drawn from a 7-year prospective cohort study conducted in China[24]. Although this topic has received widespread attention, few studies have investigated the effect of depression on sarcopenia. Overall, our MR study provided evidence that depression and sarcopenia are possibly connected in a bidirectional manner, whereas previous studies primarily focused on investigating the effect of depression on sarcopenia in a unidirectional manner.

The exact mechanism between depression and sarcopenia remains inconclusive. However, there are several potential connections between the two conditions. First, in the original GWAS of hand grip strength, expression quantitative trait loci analyses revealed multiple genes associated with neurodevelopmental disorders or brain function[14]. The results of a meta-analysis demonstrated a significant enrichment of gene expression of brain-related transcripts[14]. In another study, researchers used twin data from China to explore the genetic overlap between depression and grip strength[25]. They observed potential genetic correlations, SNPs, genes, and pathways common to both conditions, which indicates a shared genetic basis[25]. Second, some studies have suggested that brain-derived neurotrophic factor secreted by skeletal muscle may play a role in depression and anxiety[10]. Brain-derived neurotrophic factor drives hippocampal neurogenesis, and the hippocampus is a key region of the brain implicated in psychiatric illness[26]. Third, chronic inflammation could potentially serve as a shared risk factor for both depression and sarcopenia[27]. Inflammatory biomarkers,

such as C-reactive protein and interleukin 6, are negatively associated with ALM[28]. Meanwhile, increased C-reactive protein and interleukin 6 are also associated with future depression[29]. This could be attributed to increased inflammatory cytokines in patients with sarcopenia, which could negatively impact the central nervous systems of older adults leading to a depressed mood and reduced mobility[27]. Finally, patients with depression are typically lacking in physical activity, which is a well-known factor leading to sarcopenia[30]. These findings collectively supported the conclusion of our current MR analysis, indicating a bidirectional relationship between depression and sarcopenia.

One of the key strengths of this analysis was the utilization of well-powered GWAS data for depression and sarcopenia-related traits. The implementation of a bidirectional MR design allowed for a comprehensive evaluation of the mutually causal relationship. Nevertheless, there are several limitations that need to be addressed. First, sample overlap between the exposure and outcome populations might potentially influence the study results. There was also a study, however, supporting the applicability of a single large dataset from large biobanks in two-sample MR studies[31]. Second, ALM was not directly measured by the BIA equipment but was estimated based on whole-body electrical conductivity. The estimates of BIA can be influenced by factors such as age, ethnicity, hydration status, and other related discrepancies. All of these factors may subsequently influence the MR results. Third, in the original GWAS the authors reported that they used the broad definition of depression in the cohort of the UK Biobank. This reporting mechanism differed from the self-declared clinical depression phenotype of the 23andMe_307k cohort and the clinically obtained phenotype of the PGC_139k cohort. This difference may have an impact on the results of the MR analysis. Fourth, the population in our study was restricted to Europe, which limits the generalizability of our findings to non-European populations. Finally, potential directional pleiotropy may contribute to bias in the estimation of causal inference even though MR-Egger regression and MR-PRESSO methods were applied.

CONCLUSION

We provided evidence of a bidirectional association between depression and sarcopenia. Depression was causally related to decreased muscle mass. Meanwhile, declined muscle strength might lead to a higher risk of depression. Our study highlighted the importance of assessing sarcopenia and depression among older adults to understand and address the interplay between physical and mental health.

ARTICLE HIGHLIGHTS

Research background

Sarcopenia is a complex geriatric disorder marked by a gradual and progressive reduction of skeletal muscle mass, decrease in skeletal muscle strength, and deterioration in physical performance. Depression is also common among the elderly. Observational studies have suggested that depression is associated with sarcopenia.

Research motivation

The causal relationship between depression and sarcopenia remains unclear.

Research objectives

To investigate the causal relationship between depression and sarcopenia.

Research methods

We performed a Mendelian randomization (MR) analysis to identify the bidirectional relationship between depression and sarcopenia-related traits. Summary-level data and independent variants were used as instrumental variables that came from large genome-wide association studies of depression (414055 cases and892299 controls), of appendicular lean mass (ALM, 450243 participants), and of hand grip strength (exposures: 360000 participants; outcomes: 334925 participants).

Research results

We identified a negative association of depression with lower ALM. In the reverse MR analysis, we also observed an inverse association of hand grip strength with depression. Similar results were obtained in the sensitivity analyses.

Research conclusions

Depression was causally related to decreased muscle mass. Declined muscle strength might lead to a higher risk of depression.

Research perspectives

Our findings highlighted a potential bidirectional relationship between depression and sarcopenia with implications for both mental and physical health.

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FOOTNOTES

Author contributions: Wang DK and Li YH drafted the initial manuscript, analyzed the data, and interpreted the results; Guo XM designed the study, analyzed the data, and critically revised the manuscript; All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Safety and effectiveness of lurasidone in the treatment of Chinese schizophrenia patients: An interim analysis of post-marketing surveillance

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Abstract

BACKGROUND

Schizophrenia is a psychiatric disorder characterized by chronic or recurrent symptoms. Lurasidone was licensed in China in 2019 for the treatment of adult schizophrenia in adults with a maximum dose of 80 mg/d. However, post-market surveillance (PMS) with an adequate sample size is required for further validation of the drug's safety profile and effectiveness.

AIM

To conduct PMS in real-world clinical settings and evaluate the safety and effectiveness of lurasidone in the Chinese population.

METHODS

A prospective, multicenter, open-label, 12-wk surveillance was conducted in mainland China. All patients with schizophrenia from 10 sites who had begun medication with lurasidone between September 2019 and August 2022 were eligible for enrollment. Safety assessments included adverse events (AEs), adverse drug reactions (ADRs), extrapyramidal symptoms (EPS), akathisia, use of EPS drugs, weight gain, and laboratory values as metabolic parameters and the QTc interval. The effectiveness was assessed using the brief psychiatric rating scale (BPRS) from baseline to the end of treatment.

RESULTS

A total of 965 patients were enrolled in the full analysis set and 894 in the safety set in this interim analysis. The average daily dose was 61.7 ± 19.08 mg (mean ± SD) during the treatment. AEs and ADRs were experienced by 101 patients (11.3%) and 78 patients (8.7%), respectively, which were mostly mild. EPS occurred in 25 individuals with a 2.8% incidence, including akathisia in 20 individuals (2.2%). Moreover, 59 patients received drugs for treating EPS during the treatment, with an incidence of 6.6% which dropped to 5.4% at the end of the treatment. The average weight change was 0.20 ± 2.36 kg (P = 0.01687) with 0.8% of patients showing a weight gain of ≥ 7% at week 12 compared with that at the baseline. The mean values of metabolic parameters and the QTc interval at baseline and week 12 were within normal ranges. The mean changes in total BPRS scores were -8.9 ± 9.76 (n = 959), -13.5 ± 12.29 (n = 959), and -16.8 ± 13.97 (n = 959) after 2/4, 6/8, and 12 wk, respectively (P < 0.001 for each visit compared with the baseline) using the last-observation-carried-forward method.

CONCLUSION

The interim analysis of the PMS of adult patients with schizophrenia demonstrate the safety and effectiveness of lurasidone in the Chinese population. No new safety or efficacy concerns were identified.

Key Words: Lurasidone; Safety; Effectiveness; Surveillance; Schizophrenia; Chinese

Core Tip: We conducted the first post-marketing surveillance of the actual use of lurasidone in the treatment of patients with schizophrenia in real-world clinical practice since the drug was licensed in mainland China in 2019, and evaluated the safety profile and effectiveness of lurasidone in Chinese population. Here, we report an interim analysis based on 965 patients who received the medication between 2019 and 2022. This study hold significance as it contributes additional safety and effectiveness data on lurasidone beyond what was gathered in pre-marketing trials. Furthermore, it provides valuable reference information for clinical decision-making of schizophrenia treatment.

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INTRODUCTION

Schizophrenia is a psychiatric disorder marked by chronic or recurrent symptoms, often resulting in an impairment of social and occupational functioning. The characteristics of schizophrenia typically include incoherent or illogical

thoughts, delusions, hallucinations, unusual behaviors, and cognitive impairment[1]. Its global prevalence is approximately 1%, with an incidence of about 1.5 per 10000[2]. It is a highly disabling and costly condition, ranking among the top 10 burdensome diseases[3].

The goal of schizophrenia treatment is to reduce acute symptoms and prevent recurrence while maximizing the patient's quality of life[4]. Lurasidone is a second-generation antipsychotic drug with a high affinity for dopamine D_2, serotonin 5-$HT_{2A,}$ and 5-HT_7 receptors and a low affinity for H_1 and 5-HT_{2C} receptors. It is considered to be associated with relatively less side effects[5-7].

Lurasidone was licensed in mainland China in 2019 for the treatment of schizophrenia in adults, with a maximum dose of 80 mg/d. A series of clinical studies have been conducted to verify its efficacy and safety[8,9] and numerous clinical experiences have been accumulated for Chinese patients with schizophrenia since the launch. However, a post-market surveillance (PMS) for the drug with an adequate sample size is also required by the Chinese government. This study thus aimed to conduct a surveillance of the actual use of lurasidone among Chinese patients with schizophrenia in real-world clinical practice and evaluate the safety profile and effectiveness of the drug in the Chinese population. Here, we report an interim analysis based on 965 patients who received lurasidone between 2019 and 2022.

MATERIALS AND METHODS

Study design and population

This study represents an interim analysis of a 12-wk, prospective, observational, multi-center, open-label PMS conducted in China. Patients with schizophrenia from 10 sites across China who had begun treatment with Latuda® between September 2019 and August 2022 were enrolled. The patients were required to provide informed consent before participating. An electronic data capture system was used for the collection of diagnostic and treatment information such as details on drug use, adverse events (AEs), and other related parameters including but not limited to laboratory examinations. All patients who met the inclusion requirement were included in the full analysis set (FAS), whereas the safety set (SS) consisted of patients who had received at least one treatment and had data on safety indicators recorded after the treatment. The study protocol was approved by the ethics committees of Shanghai Mental Health Center (the leading site) and other sites.

Dose and concomitant therapy

The administered dose of lurasidone was decided by the treating physicians, typically initiating at 40 mg/d with no requirement for titration. Depending on the treatment response and tolerability, the dose could be increased to a maximum daily dose of 80 mg/d, according to the approved prescribing information in China (a dose of 160 mg/d is approved overseas). Because this study was non-interventional, concomitant therapy deemed essential by the physician was permitted and reported on the electronic Case Report Form, including but not limited to antipsychotic drugs, mood stabilizers, antidepressants, anxiolytics, and antiepileptics.

Safety evaluation

Safety analyses were based on the SS and evaluated by the frequency and severity of AEs that occurred during the trial. AEs were coded according to the International Council for Harmonisation International Dictionary of Medical Terms (MEDDRA 24.0, Medical Dictionary for Regulatory Activities). Assessments were made at visit 1 (week 0), visit 2 (weeks 2-4), visit 3 (weeks 6-8), and visit 4 (week 12) and were reported by the treating physicians. The assessment included the incidence of total AEs, extrapyramidal symptoms (EPS), akathisia, use of EPS drugs, and mean changes in weight from baseline. Adverse drug reactions (ADRs) were defined as AEs for which the participating physicians could not rule out lurasidone as the cause.

Effectiveness evaluation

The assessment of effectiveness was based on FAS and assessed by the change in the overall brief psychiatric rating scale (BPRS) score relative to the baseline at weeks 2-4/ weeks 6-8, and week 12. The BPRS is a scale that was created to assess clinical changes in patients with schizophrenia, with 18 items designed to represent discrete symptom areas. Items are rated on a 7-point Likert scale, from 1 = "not present" to 7 = "extremely severe", with the total scores ranging from 18 to 126 (calculated by summation of the item scores). The BPRS evaluates five areas: Anxiety-depression, anergia, thought disturbance, activation, and hostility-suspiciousness. Scores for the 5-factor model were also calculated[10].

Statistical analysis

The data were in the form of descriptive statistics as the study was non-interventional and were analyzed using R software version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are presented as frequencies and proportions and shown as *n* (%). Continuous variables are presented as mean ± SD and compared using paired *t*-tests, with $P < 0.05$ indicating statistical significance. Effectiveness endpoint data were analyzed using the last-observation-carried forward (LOCF) approach for the missing values.

Biostatistics statement

The statistical methods of this study were reviewed by a member of the Biostatistical Service from the Shanghai Medical Insight Technology Co., Ltd.

RESULTS

Patient characteristics and baseline demographics

A total of 965 participants were enrolled in the FAS. The SS comprised 894 participants after excluding 71 patients owing to a lack of AE documentation (Figure 1).

The baseline demographics showed that 39.2% of the patients were male and 60.8% were female. The average age was 35.4 ± 14.27 years and 7.5% of the patients were aged < 18 years. The average height was 166.1 ± 7.97 cm and average body weight was 66.0 ± 13.86 kg. Overall, 55.3% of the patients had obtained antipsychotic medication within 1 mo prior to the baseline (Table 1).

Dosing and concomitant medication

In the FSA comprising 965 patients, the mean exposure level of lurasidone was 5547.5 ± 3477.04 mg with 88.4 ± 40.98 exposure days and an average daily dose of 61.7 ± 19.08 mg during treatment. A total of 57.3% of the 949 participants in the FAS received concomitant medication during the surveillance, comprising drug (n = 520, 54.8%) and non-drug (n = 156, 16.4%) therapies. The number and proportion of patients in each treatment category are detailed in Table 2.

Safety of lurasidone

Overall, 101 (11.3%) and 78 (8.7%) of the 894 patients in the SS cohort developed AEs and ADRs, respectively. Most of these were mild AEs (n = 87, 9.7%) and ADRs (n = 65, 7.3%). Fourteen (1.6%) and 12 (1.3%) patients developed AEs and ADRs, respectively, prompting discontinuation, whereas the presence of SAEs was only reported in one patient (Table 3). According to the System Organ Class (SOC) classification, the most common SOC AEs were investigations and nervous system disorders, and the most frequent AEs were akathisia (n = 22, 2.5%), blood prolactin increased (n = 21, 2.3%), and nausea (n = 9, 1.0%) (Supplementary Table 1).

EPS: EPS ADRs occurred in 25 patients (2.8%); of these, 2.2% experienced akathisia, 0.8% acute dystonia, and 0.2% parkinsonism, as demonstrated by the subgroup analysis. No reports of tardive dyskinesia or other EPS ADRs occurred during treatment (Table 4).

Use of EPS drugs: In the SS, 59 of 894 participants used EPS drugs to reduce the incidence and severity of extrapyramidal side effects during the treatment period. The incidence was 6.6%, which dropped to 5.4% at the end of the treatment. The most frequent EPS drug used was Benzhexol, which was used by 46 patients (5.1%).

Weight gain: The mean body weights of the patients at baseline and week 12 were 66.21 ± 14.01 kg and 66.21 ± 13.70 kg, respectively, resulting in a mean weight change of 0.20 ± 2.36 kg. This weight change demonstrated statistical significance in the intra-group comparison (P = 0.0168). Furthermore, 7 (0.8%) patients were found to have gained ≥ 7% of their weight at visit 4 (Table 5).

Laboratory values: The mean values of glutamic-pyruvic transaminase (GPT), glutamic oxaloacetic transaminase, serum creatinine, fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and QTc interval were within normal ranges at baseline and had not significantly changed when measured at the week 12 visit, except for GPT (P = 0.0189) (Table 6).

Effectiveness of lurasidone

The changes observed in the total BPRS score indicated a significant improvement in the severity of schizophrenia throughout the course of the treatment. The total BPRS score stood at 43.6 ± 15.28 (n = 959) at baseline. Over the course of treatment, it progressively decreased to 34.7 ± 12.22 (n = 959), 30.1 ± 10.68 (n = 959), and 26.8 ± 9.58 (n = 959), respectively, at 2/4, 6/8, and 12 wk, with overall mean changes of -8.9 ± 9.76, -13.5 ± 12.29, and -16.8 ± 13.97, respectively (P < 0.001 for each visit compared with the baseline) based on the LOCF method. The changes in the 5-factor model scores exhibited a similar trend as the total BPRS score, with highly significant reductions in the score observed on each visit (P < 0.001) (Table 7).

DISCUSSION

Lurasidone is a novel benzisothiazole antipsychotic drug that was authorized by the FDA in 2010 for the treatment of adult patients with schizophrenia[5] and has been licensed in many other countries, including China in 2019. Numerous pre-marketing trials have been conducted, which have demonstrated the efficacy and safety of lurasidone[8,11-13]. However, pre-marketing research has limitations. These include a small sample size, difficulties in detecting AEs with low incidence but high severity during the trial phase, and relatively strict participant inclusion and exclusion criteria, preventing the participation of certain patients with specific diseases in the trials. Thus, safety issues may not be fully identified and the use of concomitant medication tends to be controlled, which is inconsistent with real-world clinical practice. The use of PMS is thus important to further evaluate the safety and effectiveness of drugs. This study represents the initial PMS of lurasidone conducted in a Chinese population. The interim analysis confirmed that lurasidone was effective, generally safe, and well-tolerated as a treatment option for schizophrenia in adult Chinese patients.

Table 1 Baseline demographics and clinical characteristics (*n* = 965)

Background factor	Category	*n* (%)
Sex	Male	378 (39.2%)
	Female	587 (60.8%)
Age	mean ± SD	35.4 ± 14.27
	< 18 yr	72 (7.5%)
	18 yr	892 (92.5%)
Height (cm)	mean ± SD	166.1 ± 7.97
Weight (kg)	mean ± SD	66.0 ± 13.86
Months since onset of first episode	mean ± SD	92.6 ± 113.95
Months since onset of current episode	mean ± SD	5.8 ± 55.52
Baseline BPRS score	mean ± SD	43.6 ± 15.28
Comorbidity of mental disorder besides schizophrenia	Yes	958 (99.3%)
Comorbidity besides mental disorder	Yes	848 (88.1%)
Antipsychotic medication within 1 mo prior to baseline	Yes	532 (55.3%)

BPRS: Brief psychiatric rating scale.

Table 2 Concomitant therapy (*n* = 949[1])

Category	*n*	%
All	544	57.3
Pharmacological therapy	520	54.8
Oral antipsychotic drugs	434	45.7
Injectable antipsychotics	12	1.3
Sedative-hypnotics/EPS drugs	112	11.8
Mood stabilizers/antiepileptic drugs	39	4
Antidepressants/anxiolytics	61	6.4
Other categories	105	11.0
Non-pharmacological therapy	156	16.4
ECT	12	1.3
rTMS	14	1.5
Other categories	142	15

[1]*n* = 949, number of patients in the full analysis set with concomitant therapy data documentation.
EPS: Extrapyramidal symptoms; ECT: Electroconvulsive shock therapy; rTMS: Repetitive transcranial magnetic stimulation.

Common adverse reactions of lurasidone include akathisia, EPS, somnolence, and nausea[14,15]. The most frequent treatment-emergent AEs (TEAEs) among Asian participants during a 6-wk study were found to be headache, constipation, akathisia, and nausea, with the latter two being more common in the 80 mg/d group compared with that in the 40 mg/d group[16]. During 26 wk of open-label extension treatment with lurasidone, the most frequently observed TEAEs were EPS, insomnia, akathisia, nasopharyngitis, schizophrenia, anxiety, nausea, and headache[17]. In the current PMS, the most frequently reported AEs included akathisia, elevated blood prolactin levels, and nausea, with the majority of the cases characterized as mild in severity. The pattern of AEs/ADRs identified in this interim analysis closely resembled the AE/ADR profile with the use of lurasidone 40 mg/d in previous trials for the treatment of schizophrenia [13]. The most frequently employed measures in response to EPS ADRs involve reduction of the antipsychotic drug, transitioning to antipsychotic drugs with a lower propensity to induce EPS, or utilization of specific medications designed for EPS treatment. In this study, the proportion of EPS drugs used during the treatment was 6.6%, which was higher than the incidence of EPS ADR (2.8%). The primary reasons for this could be attributed to two factors: (1) EPS treatment

Table 3 Summary of adverse events and adverse drug reactions (*n* = 894)

Category	*n*	%
Any AE	101	11.3%
Any ADR	78	8.7%
AE leading to discontinuation	14	1.6%
ADR leading to discontinuation	12	1.3%
EPS AE	29	3.1%
EPS ADR	25	2.7%
EPS AE leading to discontinuation	3	0.3%
EPS ADR leading to discontinuation	3	0.3%
Serious AE	1	0.1%
Serious ADR	1	0.1%

AE: Adverse event; ADR: Adverse drug reactions; EPS: Extrapyramidal symptoms.

Table 4 Percentage of participants with extrapyramidal symptom adverse drug reactions (*n* = 894)

Category	*n*	%
All	25	2.8%
Acute dystonia	7	0.8%
Akathisia	20	2.2%
Parkinsonism	2	0.2%
Tardive dystonia	0	0.0%
Other EPS ADR	0	0.0%

EPS: Extrapyramidal symptoms; ADR: Adverse drug reactions.

Table 5 Summary of weight gain (*n* = 894)

	Total
Baseline (mean ± SD)	66.21 ± 14.01
12 weeks (mean ± SD)	66.21 ± 13.70
Change in body weight (mean ± SD)	0.20 ± 2.36[1]
Weight gain from baseline ≥ 7%, *n* (%)	7 (0.8%)

[1]$P < 0.05$.

induced by antipsychotic drugs other than lurasidone in participants who were administered concomitant antipsychotics (47%); and (2) the utilization of prophylactic medications aimed at preventing patients from developing EPS during the course of treatment. The latter strategy is mainly aimed at patients who are susceptible to EPS (patients in the early stages of treatment and young males), to reduce their discomfort and improve compliance.

Lurasidone exhibits a strong affinity for dopamine D_2, 5-HT_7, and serotonin 5-HT_{2A} receptors. This favorable D_2/5HT_{2A} balance not only ensures the drug's antipsychotic effectiveness but also helps mitigate the EPS resulting from D_2 blockade [18]. Thus, as with other atypical agents, lurasidone has antipsychotic effects with limited EPS risk[14,19,20]. The incidence of EPS-related events (excluding akathisia and restlessness) was found to be 14.7% for lurasidone and 5.1% for placebo in short-term clinical trials[15]. In two long-term trials, the proportions of participants reporting EPS AEs in the lurasidone group during 12 mo of treatment were 12.9% and 11.9%, respectively[21,22].

Akathisia is one of the most frequent ADRs observed in multiple trials conducted in different regions. In a pooled analysis of European data from three randomized controlled trials (RCTs), the incidence of akathisia was 11.3%, representing 8.1% in the 40–80 mg/d group and 15.8% in the 120–160 mg group[23]. In the Asian population, the proportion of

Table 6 Changes in laboratory values from baseline to week 12

Measure	*n*	Mean	SD
GPT (U/L)			
Baseline	376	25.14	21.548
Week 12	109	27.33	20.624
Mean change	93	5.38[1]	21.705
GOT (U/L)			
Baseline	363	22.19	12.715
Week 12	108	24.39	12.565
Mean change	92	0.96	16.625
Serum creatinine (μmol/L)			
Baseline	370	65.86	16.383
Week 12	106	69.26	14.695
Mean change	90	1.21	10.854
Fasting blood glucose (mmol/L)			
Baseline	368	5.478	1.536
Week 12	101	5.451	1.5486
Mean change	84	-0.162	1.4467
Total cholesterol (mmol/L)			
Baseline	363	4.501	1.0389
Week 12	101	4.551	1.0888
Mean change	83	-0.079	1.1075
Triglycerides (mmol/L)			
Baseline	362	1.589	1.3002
Week 12	101	1.655	0.8413
Mean change	82	-0.207	1.3234
HDL cholesterol (mmol/L)			
Baseline	359	1.287	0.365
Week 12	99	1.308	0.3959
Mean change	82	0.073	0.415
LDL cholesterol (mmol/L)			
Baseline	344	2.694	0.8467
Week 12	90	2.746	0.7907
Mean change	73	-0.086	0.7312
QTc interval (ms)			
Baseline	280	415.6	93.41
Week 12	71	402	29.32
Mean change	57	-0.2	35.76

[1]$P < 0.05$.

GPT: Glutamic pyruvic transaminase; GOT: Glutamic oxaloacetic transaminase; HbA1c: Glycosylated hemoglobin; LDL: Low-density lipoprotein; HDL: High density lipoprotein.

Table 7 Change from baseline to week 12 (last-observation-carried forward) in the total brief psychiatric rating scale score and 5-factor model score

BPRS (mean ± SD)	Baseline (*n* = 959)	2/4 wk (*n* = 959)	6/8 wk (*n* = 959)	12 wk ± 14 d (*n* = 959)
Total score	43.6 ± 15.28	34.7 ± 12.22	30.1 ± 10.68	26.8 ± 9.58
Change in total score	-	-8.9 ± 9.76[1]	-13.5 ± 12.29[1]	-16.8 ± 13.97[1]
Anxiety-depression	9.3 ± 4.00	7.6 ± 3.20	6.7 ± 2.75	6.0 ± 2.45
Change in anxiety-depression score	-	-1.6 ± 2.40[1]	-2.6 ± 2.94[1]	-3.3 ± 3.42[1]
Anergia	8.9 ± 3.55	7.5 ± 3.01	6.7 ± 2.75	6.2 ± 2.47
Change in anergia score	-	-1.4 ± 2.28[1]	-2.2 ± 2.69[1]	-2.8 ± 3.00[1]
Thought disturbance	10.7 ± 4.40	8.3 ± 3.49	7.1 ± 3.07	6.2 ± 2.79
Change in thought disturbance score	-	-2.4 ± 3.03[1]	-3.7 ± 3.77[1]	-4.5 ± 4.15[1]
Activation	5.9 ± 3.10	4.7 ± 2.35	4.2 ± 1.86	3.8 ± 1.58
Change in activation score	-	-1.2 ± 2.01[1]	-1.7 ± 2.41[1]	-2.1 ± 2.70[1]
Hostility-suspiciousness	8.8 ± 3.93	6.5 ± 2.85	5.4 ± 2.47	4.6 ± 2.17
Change in hostility-suspiciousness score	-	-2.3 ± 2.81[1]	-3.4 ± 3.42[1]	-4.1 ± 3.77[1]

[1]$P < 0.001$(paired *t*-test).

n = 959: Number of patients in the full analysis set with brief psychiatric rating scale data.

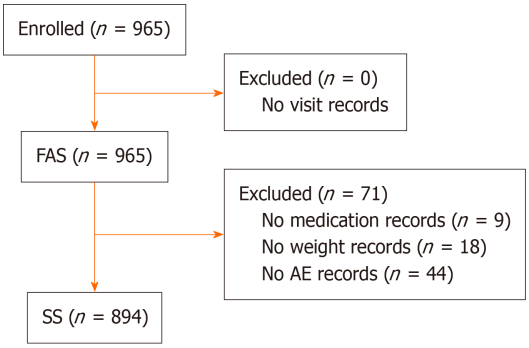

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Figure 1 Patient disposition. AE: Adverse event; FAS: Full analysis set; SS: Safety set.

patients that experienced akathisia was found to be 7.3% and 10.4% in the 40 and 80 mg/d groups, respectively, in another RCT that included mostly patients from East Asia[16]. In Chinese patients, the incidence of akathisia was reported to be 7.2% and 13.6% in patients treated separately with lurasidone and risperidone, respectively, by a pre-marketing RCT[8]. In the current PMS, the incidence of EPS ADRs was 2.8%; of these, 2.2% was contributed by akathisia, which is lower than the rates reported in previous studies. It is speculated that this inconsistency may result from three factors. First, the dosage of the drug. The development of akathisia was found to be dose-dependent in a previous trial [13]. In the current surveillance study, the average daily dose of lurasidone was 61.7 ± 19.08 mg, which is relatively low and, importantly, unlike pre-marketing clinical studies where fixed doses are commonly used, the treatment dosage in this PMS could be adjusted by the physicians based on the patient's tolerance, which may also help in reducing the occurrence of ADRs. Second, the concomitant medication. Drugs for treating EPS were allowed in the present study owing to its observational design of real-world clinical practice, and these medications may have led to reduced EPS and akathisia side effects. Last, sample size and monitoring requirements. Compared with pre-marketing RCTs, PMS studies typically entail larger sample sizes and involve less stringent monitoring protocols, which may occasionally result in a relatively lower proportion of AEs/ADRs reported by the participating physicians. However, a direct comparison of the data between these studies is generally not appropriate owing to differences in eligibility criteria and study methods.

Weight gain has been demonstrated to be a risk factor for treatment non-adherence in patients with schizophrenia[24,25] as it results in a worse quality of life, social exclusion, and increased stigma[26]. Moreover, a higher risk of developing metabolic syndrome (MetS) is linked to increased body weight[27,28]. A network meta-analysis of 100 RCTs comprising 25952 patients with schizophrenia found evidence of weight gain associated with the use of nine antipsychotics[29]. The reason why antipsychotic drugs induce weight gain remains unclear but might partly be ascribed to 5-HT_{2C}- and H_1-receptor affinity, which leads to hyperphagia and increased food intake[30,31]. However, lurasidone has only weak

affinity for 5-HT_{2C} receptors and poor or no affinity for histamine H_1[32]. Thus, the risk of weight gain might be relatively low from a mechanistic perspective, as confirmed by multiple clinical trials[33,34]. For short-term outcomes, 15 antipsychotic medications were evaluated for their effectiveness and tolerability by a meta-analysis of 212 trials and it was found that lurasidone, compared with placebo, is one of the only three drugs that did not lead to increased weight gain[33]. In terms of long-term outcomes, a pooled analysis of six studies showed that the mean weight change at month 12 was significantly greater in patients treated with risperidone and quetiapine extended-release (quetiapine XR) than those with lurasidone (+ 2.6 kg, + 1.2 kg *vs* − 0.4 kg)[34]. Previous trials did not find a dose-response relationship between the drugs and weight gain [11-13,16], and Wu *et al*[35] observed that the dose-response curve plateaued at 60 mg/d in a dose-response meta-analysis of 97 studies. In the current PMS, although the body weights of the patients at week 0 and week 12 were remarkably close (66.21 ± 14.010 kg *vs* 66.21 ± 13.696 kg), the number of participants with weight data recorded at these two visits varied (888 *vs* 801). Therefore, we used paired *t*-tests to analyze the mean change in weight, which was found to be 0.20 ± 2.356 kg at week 12 compared with the baseline paired population, showing a significant difference (P = 0.0168). However, this change remained minimal, and only 0.8% of patients showed a weight gain of ≥ 7% from baseline to week 12. Overall, in line with prior studies, there was a low chance of clinically significant weight gain in patients treated with lurasidone according to the results of the current PMS.

MetS is a collection of clinical and laboratory findings that are associated with an increased risk of cardiovascular disease[36]. The causes of MetS in patients with schizophrenia are not entirely elucidated, with antipsychotic drug side effects being a considered contributing factor[37]. Second-generation antipsychotics appear to be more likely to cause metabolic disturbances than first-generation antipsychotics, probably because of their affinity for the $5HT_{2C}$- and H_1-receptors as well as the M3 receptors that regulate the release of insulin, and thus maintain glucose homeostasis[37,38]. Previous studies have found that lurasidone is associated with a relatively low incidence of MetS[39,40]. The odds of developing MetS during the study period were significantly lower in patients receiving lurasidone than those treated with olanzapine and quetiapine XR in short-term treatment, and risperidone in long-term treatment, as demonstrated by a pooled analysis[41]. Despite the lack of a control group, the metabolic parameters of the study participants recorded at each visit in the current PMS were predominantly within the normal range, and a high proportion of those who were normal at baseline continued to remain normal during further follow-up visits (data not shown). This supports previous findings that lurasidone treatment has limited risk for adverse metabolic effects.

Hyperprolactinemia may be developed in patients with schizophrenia with or without antipsychotic medication[42]. Elevated prolactin levels induced by antipsychotic drugs are mainly associated with D_2 receptor affinity[43]. Several short-term studies have found no evidence of clinically significant changes in prolactin levels in patients treated with lurasidone[11-13]. A multicenter RCT conducted in mainland China showed that compared with the risperidone-treated group, the incidence of increased prolactin was remarkably lower in the lurasidone-treated group (3.1% *vs* 14.1%)[8]. In the current PMS, the incidence of increased prolactin was 2.3%, verifying that lurasidone has limited effects on prolactin levels, consistent with prior studies.

Lurasidone is a full antagonist of the dopamine D_2 receptor, with a receptor occupancy ratio of the latter after taking lurasidone 40 mg/d of 60%–80%, which is a prerequisite for its antipsychotic effectiveness[6]. Its targeting of the 5-HT_7 receptors can potentially enhance cognition by improving emotional regulation and sensory processing[6]. For acute phase treatment, a post hoc analysis of five studies in patients with acute schizophrenia found that lurasidone can reduce agitation early and sustainably, as measured by the PANSS-EC score[44]. Another meta-analysis of eight short-term RCTs confirmed that lurasidone was superior to placebo irrespective of positive or negative symptoms[45]. For maintenance treatment, an extension trial of 6 mo following a 6-wk acute-phase treatment of lurasidone showed further reduction and stabilization of the total PANSS score after receiving a flexible dose of lurasidone[46]. In terms of mood disorder, a pooled analysis of four studies verified significant improvement in depressive symptoms by lurasidone with greater decreases in MADRS score[47]. Overall, previous studies have supported the effectiveness of lurasidone in the treatment of schizophrenia and the interim analysis of the current PMS confirmed this conclusion, as supported by the continuous decrease in the total BPRS and the 5-factor model scores across all four visits during the surveillance period.

This study has some limitations. It was a single-armed, observational study with no control group, and the use of concomitant therapy, such as antipsychotic and EPS drugs, was allowed, which may represent confounders to the analysis and interpretation of the results. The sample sizes at each visit varied significantly and several participants did not provide their complete information, especially at visits 2 and 3. This may have an impact on the average of the measured data values and may not reflect the actual changes in the patients' condition. Although we used paired *t*-tests to partially address this issue, bias remains inevitable. The study period of this interim analysis was only 12 wk, and thus some AEs/ADRs that require a relatively long time to manifest may have not been observed and recorded during this period. It is worth mentioning that the study will be followed by a 12-month extension period, which we believe will provide further data support for clinical applications.

CONCLUSION

This preliminary data analysis from the PMS of lurasidone in adult patients with schizophrenia demonstrated its safety and effectiveness in a Chinese population, without emergence of any novel safety or efficacy issues. The study is ongoing and will facilitate continue to provide additional data and insights into the characteristics of lurasidone and its practical application in clinical settings.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a psychiatric disorder characterized by chronic or recurrent symptoms. Lurasidone was licensed in China in 2019 for the treatment of adult schizophrenia in adults.

Research motivation

To further validate the safety profile and effectiveness of lurasidone.

Research objectives

To evaluate the safety and effectiveness of lurasidone in the Chinese population.

Research methods

We conducted a prospective, multicenter, open-label, 12-wk surveillance in mainland China, and reported the interim analysis based on 965 patients who received the medication between 2019 and 2022.

Research results

Mean changes in total brief psychiatric rating scale scores were -8.9 ± 9.76 (n = 959), -13.5±12.29 (n = 959), and -16.8 ± 13.97 (n = 959) after 2/4, 6/8, and 12 wk, respectively (P < 0.001 for each visit compared with the baseline) using the last-observation-carried-forward method. adverse events and adverse drug reactions were experienced by 101 (11.3%) and 78 patients (8.7%), respectively, which were mostly mild.

Research conclusions

The interim analysis of the post-market surveillance demonstrate the safety and effectiveness of lurasidone in the Chinese population.

Research perspectives

This study contributes additional safety and effectiveness data on lurasidone, surpassing those obtained in pre-marketing trials. It offers essential guidance for clinical decision-making in the treatment of schizophrenia.

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FOOTNOTES

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ORIGINAL ARTICLE

Prospective Study

Treatment outcomes and cognitive function following electroconvulsive therapy in patients with severe depression

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Abstract

BACKGROUND

Traditional treatments for major depressive disorder (MDD), including medication and therapy, often fail and have undesirable side effects. Electroconvulsive therapy (ECT) uses electrical currents to induce brief seizures in the brain, resulting in rapid and potent antidepressant effects. However, owing to misconceptions and controversies, ECT is not as widely used as it could and often faces stigmatization.

AIM

To evaluate the efficacy and safety of ECT compared to those of medication and/or therapy in patients with severe MDD.

METHODS

This prospective cohort study included 220 individuals with severe MDD who were divided into the ECT and non-ECT groups. The patients in the ECT group underwent bilateral ECT three times a wk until they either achieved remission or reached a maximum of 12 sessions. The non-ECT group received medication and/or therapy according to clinical guidelines for MDD. The primary outcome was the variation in the hamilton depression rating scale (HDRS) score from treatment/ECT initiation to week 12. In addition, patients' quality of life, cognitive abilities, and biomarkers were measured throughout the study.

RESULTS

Although both groups showed significant improvements in their HDRS scores over time, the improvement was more pronounced in the ECT group than in the non-ECT group. Additionally, the ECT group exhibited a more substantial improvement in the quality of life and cognitive function than those of the non-ECT group. Compared with the non-ECT group, the ECT group exhibited evidently lower variations in the brain-derived neurotrophic factor (BDNF) and

cytokine interleukin-6 (IL-6) levels. The side effects were generally mild and comparable between the two groups. ECT is safer and more potent than medication and/or therapy in mitigating depressive symptoms, enhancing well-being, and bolstering cognitive capabilities in individuals with severe MDD. ECT may also affect the levels of BDNF and IL-6, which are indicators of neuroplasticity and inflammation, respectively.

CONCLUSION

ECT has emerged as a potentially advantageous therapeutic approach for patients with MDD who are unresponsive to alternative treatments.

Key Words: Alternative therapies; Biomarkers; Cognitive function; Electroconvulsive therapy; Major depressive disorder; Medication therapy

Core Tip: Electroconvulsive therapy (ECT) is more efficient and safer in treating severe major depressive disorder (MDD) compared to medication and/or therapy. Here, ECT led to more pronounced improvements in depressive symptoms, quality of life, and cognitive function than non-ECT treatments. Additionally, ECT affected biomarkers related to neuroplasticity (brain-derived neurotrophic factor) and inflammation (interleukin-6). These findings highlight the potential of ECT as a therapeutic approach for individuals with severe MDD who do not respond to conventional treatments. By providing evidence of its beneficial outcomes, this study aimed to address the stigmatization surrounding ECT and facilitate its broader adoption in clinical practice.

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INTRODUCTION

Major depressive disorder (MDD) is a prevalent mental health condition with a profound impact on many individuals worldwide. The World Health Organization reported that MDD contributes significantly to the global health burden[1]. This condition is characterized by a persistent sense of sadness, diminished interest in daily activities, and a reduction in function that lasts for at least 2 wk. MDD can negatively affect physical, psychological, social, and occupational aspects of life, leading to increased morbidity, mortality, and suicide risk[2].

Conventional treatments for MDD include pharmacotherapy and psychotherapy, which aim to restore mood balance, reduce distress, and enhance coping strategies[3]. Pharmacotherapy involves the use of antidepressants, such as serotonin, dopamine, and norepinephrine, which act by targeting neurotransmitter systems[4]. Psychotherapy comprises a variety of psychological interventions that address the cognitive, behavioral, interpersonal, and emotional factors that contribute to depression[5]. Widely practiced and documented psychotherapy techniques include cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and supportive therapy[6]. However, conventional therapies are often insufficient and associated with adverse effects. Approximately 50% of patients achieve remission after a typical course of antidepressants, and approximately 30% remain resistant to multiple types of treatment[7]. Furthermore, antidepressants can cause adverse reactions, including nausea, weight gain, sexual issues, insomnia, and agitation[8]. Psychotherapy can also be ineffective or inaccessible to some patients because of a lack of availability, affordability, or motivation. Moreover, conventional therapies may take several wks or months before significant improvements are evident[9].

Electroconvulsive therapy (ECT) is a medical procedure performed under general anesthesia, using electrical currents to induce brief seizures in the brain. ECT has been used since 1938, primarily for treating schizophrenia, and was pioneered by Cerletti and Bini[10]. ECT has been widely used to treat many psychiatric disorders, particularly severe or treatment-resistant MDD[11]. It is a highly potent and safe remedy for acute or suicidal MDD, with remission rates ranging from 60% to 90%. ECT has been shown to improve the overall well-being and mental processing abilities of patients with severe MDD[11] and can produce rapid and robust antidepressant effects, with improvements observed within 1-2 wk[12].

However, ECT remains underutilized and stigmatized owing to misconceptions and controversies. Many patients and even some healthcare professionals have negative attitudes and beliefs concerning ECT, finding it cruel, dangerous, or outdated or believing that its effects can be substituted by long-term psychotherapy or hospitalization[13]. Some of these misconceptions are based on the historical use of ECT, which involves the delivery of large amounts of electrical charge, inadequate anesthesia, and frequent sessions, resulting in severe side effects, such as memory loss, brain damage, or death. However, modern ECT is a safe, effective, and regulated treatment that involves minimizing the amount of electrical charge delivered, administering adequate anesthesia, and designing patient-centered personalized sessions, resulting in minimal side effects, including transient headaches, nausea, and confusion[14]. Modern ECT does not cause

brain damage or permanent memory loss and would not affect the personality or intelligence of patients[15].

The primary objective of the present study was to compare the efficacy and safety of ECT with those of pharmacotherapy and/or psychotherapy in patients with severe MDD. We hypothesized that ECT would be superior to pharmacotherapy and/or psychotherapy in terms of improving the hamilton depression rating scale (HDRS) scores, a validated clinician-rated outcome measure for MDD. We also hypothesized that ECT would be superior to pharmacotherapy and/or psychotherapy in improving the quality of life and cognitive function in patients with severe MDD. Brain-derived neurotrophic factor (BDNF), cytokine interleukin-6 (IL-6), and cortisol levels were also measured as biomarkers of neuroplasticity and inflammation.

MATERIALS AND METHODS

Study design and participants

This prospective cohort analysis was conducted at The First Hospital of Hebei Medical University in China between January 2021 and June 2022. The research methodology was approved by the ethics boards of all involved institutions and strictly adhered to the Declaration of Helsinki and Standards for Reporting Observational Research. All participants provided written informed consent before participating in the study.

The study recruited individuals aged ≥ 18 years who had been diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders guidelines, had an HDRS score > 24 points, were willing to participate in the study, and attended subsequent visits. The exclusion criteria included a history of allergic reaction to ECT or anesthesia, prior neurological issues, brain trauma, seizure-related disorders, substance misuse or dependency in the past 6 mo, receiving any medication that may influence the seizure threshold or cognitive abilities in the preceding month (such as anticonvulsants, benzodiazepines, or antipsychotics), pregnancy or breastfeeding, diagnosis of any other mental or physical ailment that might affect the study results, or inability to provide blood samples for biomarker evaluation.

Eligible participants were allocated to the ECT and non-ECT groups depending on their treatment approach. In the ECT group, individuals underwent ECT as routine treatment for MDD. In the non-ECT group, individuals underwent drug therapy and/or psychotherapy (without ECT) as a routine MDD treatment. The treatment group was chosen at the discretion of the attending psychiatric team based on their clinical assessment and inclination. Participants were paired across groups based on age, sex, and HDRS scores at baseline.

Interventions

Participants in the ECT group underwent bilateral ECT using an apparatus specifically designed to deliver brief pulses (Thymatron System IV; Somatics LLC, Lake Bluff, IL, United States) according to a standardized protocol[16]. The protocol commenced with an initial assessment, including physical checkups, electrocardiography (ECG), blood testing, and cognitive evaluation. ECT was performed under general anesthesia using propofol and succinylcholine. Stimulus power was estimated using titration technique and fine-tuned according to the seizure duration and quality. ECT was administered thrice a wk until remission was achieved or a maximum of 12 sessions were completed. Vital signs, oxygen levels, ECG findings, and side effects were recorded during and after each ECT session.

The non-ECT group was treated with medication and/or psychotherapy according to the clinical guidelines for the treatment of MDD[17]. Medications included antidepressants (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors), mood balancers (lithium or valproate), and supplementary agents (thyroid hormones or antipsychotics). Psychotherapy included CBT, IPT, or supportive therapy. Medication type, dosage, length of course, and the use or absence of psychotherapy were determined by the attending psychiatrists based on patient feedback and tolerance.

Both groups were advised not to use other treatments or medications that could influence their mood or cognitive function during the study period. They were also encouraged to maintain their regular lifestyle and environment and report any physical changes or side effects to the research team.

Outcomes

The main metric of interest was the change in the HDRS score between the initial assessment and 12-wk mark. The HDRS consists of 17 clinician-evaluated items that measure the intensity of depressive signs[18]. Scores on the HDRS range from 0 to 52 points, with higher scores indicating more pronounced depression. A score of ≤ 7 points on the HDRS was considered to signify remission, a reduction of ≥ 50% from the initial score was considered a response, and a reduction of < 50% was classified as non-response.

Additional outcomes of interest included changes in quality of life, cognitive capabilities, and specific biomarkers between the baseline and 12-wk assessments. The World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire[19], a 26-item tool, was used to measure participants' quality of life and covered the domains of physical well-being, mental health, interpersonal relations, and the surrounding environment. The WHOQOL-BREF scores range from 0 to 100 points, with higher scores indicating higher quality of life. The Montreal Cognitive Assessment (MoCA) [20], a concise evaluation instrument, was used to gauge cognitive function, covering the areas of attention span, memory retention, linguistic skills, executive decision-making, and spatial cognition. The MoCA scores range from 0 to 30 points, with higher scores indicating greater cognitive ability. Blood samples collected at the ECT initiation and 12-wk mark were analyzed to measure BDNF, IL-6, and cortisol levels. BDNF is crucial for neuronal survival, differentiation, and adaptability. IL-6, a cytokine that promotes inflammation, is involved in immune reactions and mood and cognitive regulation. Cortisol, a hormone associated with stress, influences the hypothalamic (pituitary) axis and neuroendocrine

mechanisms. Any adverse reactions were documented during each visit and categorized as mild, moderate, or intense based on their severity and association with the study interventions.

Sample size

The required sample size was determined based on the primary outcome, HDRS, with an anticipated clinically meaningful difference of 5 points between the groups, a standard deviation of 10 points, a significance level of 0.05, and a statistical power of 0.8. Based on these criteria, we calculated that at least 100 individuals were required in each group to discern meaningful differences. Anticipating a 10% dropout rate, a prudent sample of 110 individuals was recruited from each group, totaling 220 participants.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, United States). Data normality was rigorously verified using histograms and Kolmogorov-Smirnov tests. Comparative analyses of the groups' baseline attributes were conducted using independent t-tests or Mann-Whitney U tests for continuous data and chi-square or Fisher's exact tests for categorical data. Changes in HDRS scores and secondary outcomes from baseline to 12 wk were assessed between the groups using analysis of covariance. Differences in means and 95% confidence intervals (CIs) were calculated using descriptive statistics. Adverse events between the groups were analyzed using chi-square or Fisher's exact tests. Statistical significance was set at $P < 0.05$.

RESULTS

Participant flow and characteristics

A total of 220 participants were recruited, of whom 110 were allocated to the ECT group and 110 to the non-ECT group. The participants' progress throughout the study is shown in Figure 1. Eight participants withdrew from each group due to personal choices or were lost to follow-up, culminating in 204 participants (102 in each cohort) included in the final analysis.

Table 1 presents the baseline attributes of the participants. No significant baseline differences were observed between the groups in terms of age, sex, MDD duration, MDD type, HDRS score, WHOQOL-BREF score, MoCA score, BDNF level, IL-6 level, or cortisol level (all $P > 0.05$).

Primary outcome

Table 2 displays the changes in HDRS scores from the initial assessment to the 12-wk mark. Both groups showed notable improvements in HDRS scores over time ($P < 0.001$ for both cohorts). The enhancement was significantly greater in the ECT than in the non-ECT group ($P < 0.001$). The average change in HDRS score between the cohorts was -5.4 (95%CI: -7.8 to -3.0), suggesting a substantial improvement in the ECT group.

Recovery by 12 wk was significantly higher in the ECT than in the non-ECT group (68% *vs* 42%, $P < 0.001$). Similarly, the rate of positive response by the 12th wk was also significantly higher in the ECT cohort than in the non-ECT cohort (86% *vs* 64%, $P < 0.001$). Conversely, the rate of no response by 12 wk was significantly lower in the ECT than in the non-ECT group (14% *vs* 36%, $P < 0.001$).

Secondary outcomes

Table 2 presents the variations in the quality of life, cognitive ability, and biomarker levels from the initial assessment to the 12-wk mark. Both participant groups exhibited notable enhancements in the WHOQOL-BREF and MoCA scores over time ($P < 0.001$ for both metrics and groups). However, the ECT group displayed significantly greater enhancement than the non-ECT group for both metrics ($P < 0.05$). The average difference between the groups was 6.2 points (95%CI: 3.4 to 9.0) for the WHOQOL-BREF and 1.6 points (95%CI: 0.8 to 2.4) for the MoCA.

Both groups showed a significant decrease in BDNF levels and a significant increase in IL-6 levels over time ($P < 0.001$ for both metrics and groups). However, these changes were significantly smaller in the ECT than in the non-ECT group for both metrics ($P < 0.05$). The average differences between the groups were -5.8 units (95%CI: -9.2 to -2.4) for BDNF and -1.2 units (95%CI: -2.1 to -0.3) for IL-6. None of the groups exhibited any notable changes in cortisol levels over the study duration ($P > 0.05$) or at the 12-wk mark ($P > 0.05$).

Adverse events

Table 3 shows that there were no significant differences in the occurrence of adverse effects between the two groups ($P = 0.62$). Commonly reported adverse effects included headache, nausea, dizziness, and memory issues, all of which were generally mild and short-lived. Moreover, throughout the study duration, no severe adverse effects were documented.

DISCUSSION

This study demonstrated that ECT is safer and more effective than pharmacotherapy and/or psychotherapy in alleviating depressive symptoms, improving well-being, and boosting cognitive ability in individuals with severe MDD. ECT also

Table 1 Baseline characteristics of the participants

Variable	ECT group (*n* = 102)	Non-ECT group (*n* = 102)	*P* value
Age (yr)	46.3 ± 11.2	45.8 ± 10.9	0.69
Sex (female/male)	58/44	60/42	0.81
Duration of MDD (mo)	24.6 ±12.8	25.4 ± 13.1	0.07
Type of MDD (unipolar/bipolar)	82/20	84/18	0.76
HDRS score	28.4 ± 3.6	28.2 ± 3.7	0.72
WHOQOL-BREF score	42.6 ± 8.9	43.1 ± 9.2	0.66
MoCA score	24.8 ± 3.2	25.1 ± 3.4	0.54
BDNF level (ng/mL)	18.6 ± 5.4	18.9 ± 5.7	0.62
IL-6 level (pg/mL)	3.4 ± 1.2	3.5 ± 1.3	0.58
Cortisol level (ng/mL)	12.7 ± 4.1	12.9 ± 4.3	0.71

Values are shown as average ± deviation or count. ECT: Electroconvulsive treatment; MDD: Major depressive condition; HDRS: Hamilton depression evaluation scale; WHOQOL-BREF: World Health Organization Quality of Life-BREF Assessment; MoCA: Montreal cognitive evaluation; BDNF: Brain-derived neurotrophic factor; IL-6: Interleukin-6.

Table 2 Changes in hamilton depression evaluation scale score and secondary outcomes from baseline to 12 wk, *n* (%)

Outcome	ECT group (*n* = 102)	Non-ECT group (*n* = 102)	*P* value
HDRS score	-19.6 ± 6.4 (-69)	-14.2 ± 7.2 (-50)	< 0.001
WHOQOL-BREF score	+15.4 ± 8.7 (+37)	+9.2 ± 7.9 (+21)	< 0.001
MoCA score	+2.6 ± 1.4 (+10)	+1.0 ± 1.2 (+4)	< 0.001
BDNF level (ng/mL)	-12.8 ± 4.6 (-69)	-18.6 ± 5.8 (-98)	< 0.001
IL-6 level (pg/mL)	+2.2 ± 0.9 (+65)	+3.4 ± 1.2 (+97)	< 0.001
Cortisol level (ng/mL)	-0.2 ± 3.8 (-2)	-0.1 ± 4.1 (-1)	0.92

Values are depicted as average ± deviation with percentage alteration in brackets. ECT: Electroconvulsive treatment; HDRS: Hamilton depression evaluation scale; WHOQOL-BREF: World Health Organization Quality of Life-BREF Assessment; MoCA: Montreal cognitive evaluation; BDNF: Brain-derived neurotrophic factor; IL-6: Interleukin-6.

appears to regulate the levels of BDNF and IL-6, which are biomarkers for neuroplasticity and inflammation, respectively.

These findings concur with those of previous studies highlighting the advantages of ECT over other treatments for patients with severe MDD. A meta-analysis of 16 randomized controlled trials (RCTs) involving 1391 patients with MDD found that ECT was more effective than pharmacotherapy or placebo in inducing remission and response[21]. Another meta-analysis of nine RCTs involving 619 patients with treatment-resistant depression found that ECT outperformed pharmacotherapy and placebo ECT in reducing the signs of depression[22]. Furthermore, a systematic review of 24 studies involving 1708 patients with MDD found that ECT produced greater improvements in patient well-being and cognitive abilities than other treatments[23].

Although the precise mechanism underlying the action of ECT is unclear, it is likely related to its effects on the brain structure and function. ECT may induce neurogenesis, synaptogenesis, angiogenesis, and neurotrophic factor expression in multiple brain regions, particularly in the hippocampus, amygdala, and prefrontal cortex[24], which are involved in mood regulation, memory formation, and executive functions. ECT may also modulate neurotransmitter systems, including serotonin and dopamine, which are implicated in depression and cognition[25] and may normalize the hypothalamo-pituitary-adrenocortical axis activity and reduce the inflammatory response, both of which are associated with stress and depression[26,27].

The merits of the present study include its prospective cohort design, large sample size, use of a standardized protocol for ECT administration, use of validated and objective outcome measures, and long follow-up duration. The potential limitations of this study include its confinement to a single nation, absence of randomization and blinding of participants, potential variability in the prescribed pharmacotherapy and psychotherapy given to participants in the non-ECT group, and lack of assessment of other outcomes, such as cost-effectiveness or patient satisfaction.

Table 3 Adverse events reported by the participants, *n* (%)

Adverse event	ECT group (*n* = 102)	Non-ECT group (*n* = 102)	*P* value
Headache	32 (31)	28 (27)	0.54
Nausea	24 (24)	22 (22)	0.76
Dizziness	18 (18)	16 (16)	0.72
Memory impairment	14 (14)	12 (12)	0.69
Insomnia	10 (10)	14 (14)	0.39
Weight gain	8 (8)	10 (10)	0.63
Sexual dysfunction	6 (6)	8 (8)	0.57
Agitation	4 (4)	6 (6)	0.51
Confusion	2 (2)	2 (2)	> 0.99
Seizure prolongation[1]	2 (2)	N/A[2]	N/A[2]

Data are presented as number and percentage.
[1]Seizure prolongation was defined as a seizure duration > two min.
[2]Seizure prolongation was not applicable for the non-electroconvulsive therapy group. ECT: Electroconvulsive therapy; N/A: Not applicable.

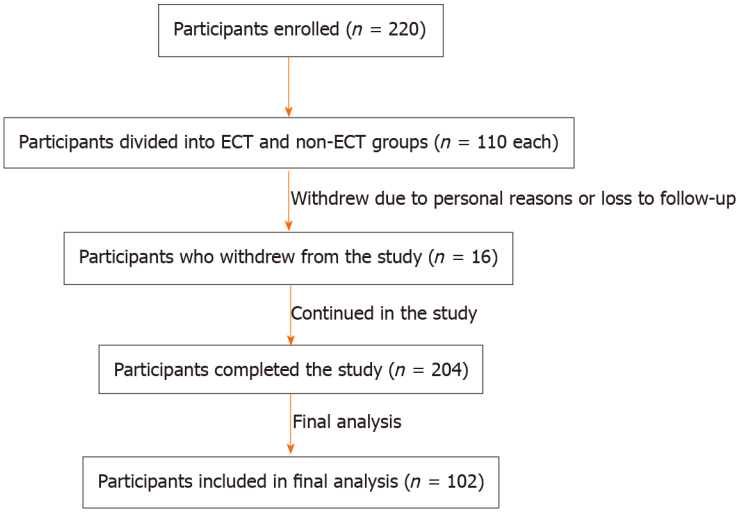

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Figure 1 Participants' progress throughout the entire research process. ECT: Electroconvulsive therapy.

CONCLUSION

In conclusion, this study demonstrated that ECT is safer and more effective than pharmacotherapy and/or psychotherapy in enhancing signs of depression, overall well-being, and cognitive abilities in individuals with severe MDD, and in modulating the levels of BDNF and IL-6, which are biomarkers of neuroplasticity and inflammation, respectively. ECT may be a valuable treatment option for patients with MDD refractory to other treatments.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) is a prevalent mental health condition characterized by persistent feelings of sadness and loss of interest. Traditional treatments for MDD, such as medications and therapy, often have limited effectiveness and can lead to undesirable side effects. Electroconvulsive therapy (ECT) is an alternative treatment that uses electrical currents to induce controlled brain seizures, resulting in rapid and potent antidepressant effects. However, ECT is associated with misconceptions, controversies, and stigmatization, which hinder its wider acceptance and utilization.

Research motivation

The main theme of this study is to evaluate the efficacy and safety of ECT compared to medication and/or therapy in patients with severe MDD. The key problems that need to be addressed are the limited effectiveness and undesirable side effects of traditional treatments for MDD, which often lead to treatment failure. Despite its rapid and potent antidepressant effects, ECT faces misconceptions, controversies, and stigmatization, resulting in its underutilization.

Research objectives

The main objective of this study was to evaluate the efficacy and safety of ECT compared to medication and/or therapy in individuals with severe MDD. The specific goals accomplished were as follows: (1) Variation in the hamilton depression rating scale (HDRS) scores between the ECT and non-ECT groups over a 12-wk period; (2) improvements in the quality of life and cognitive function between the ECT and non-ECT groups were compared; (3) variations in the levels of brain-derived neurotrophic factor (BDNF) and interleukin-6 (IL-6), potential biomarkers of neuroplasticity and inflammation, respectively, between the ECT and non-ECT groups; and (4) evaluation of the safety and tolerability of ECT compared to medication and/or therapy. The achievement of these objectives has significant implications for future research. First, it provided evidence supporting the superior efficacy and safety of the ECT as a treatment option for individuals with severe MDD who do not respond to traditional therapy. This challenges the prevailing misconceptions and stigmatization surrounding ECT and encourages further investigation and acceptance of this modality. Second, the identification of biomarkers influenced by ECT opens avenues for future studies to explore the underlying mechanisms of its antidepressant effects and potentially identify predictors of treatment response. Overall, this study contributes to optimizing therapeutic approaches for severe MDD and guides future research toward better understanding and improved treatment outcomes for affected individuals.

Research methods

A prospective cohort design was used to achieve the research objectives. The study included 220 individuals with severe MDD who were divided into the ECT and non-ECT groups. In the ECT group, bilateral ECT was administered three times a wk until remission was achieved or a maximum of 12 sessions were reached. The non-ECT group received medication and/or therapy according to clinical guidelines for MDD. The HDRS score was used as the primary outcome measure, with variations in scores assessed from the beginning to 12 wk. In addition to the HDRS score, this study measured the patients' quality of life, cognitive abilities, and biomarkers throughout the study. The biomarkers of interest were BDNF and IL-6, which are indicators of neuroplasticity and inflammation, respectively. The collected data were analyzed using appropriate statistical methods, such as t-tests or analysis of variance, to compare the outcomes between the ECT and non-ECT groups. The study also assessed the safety and tolerability of ECT compared to medication and/or therapy by monitoring and documenting any side effects experienced by the participants. The novelty of this study lies in its comprehensive evaluation of the efficacy, safety, and biomarker influences of ECT compared to conventional treatments for severe MDD. By incorporating multiple outcome measures and biomarker assessments, this study provides a holistic understanding of the effects of ECT on depressive symptoms, well-being, cognitive function, neuroplasticity, and inflammation. This prospective cohort design allows the observation of treatment outcomes over time and contributes to a growing body of evidence supporting the potential advantages of ECT as a therapeutic approach for treatment-resistant MDD.

Research results

The results of this study indicated that ECT was more effective and safer than medication and/or therapy for severe MDDs. Both the ECT and non-ECT groups showed significant improvements in the HDRS scores over the 12-wk period. However, the ECT group demonstrated a more pronounced improvement in depressive symptoms than that of the non-ECT group. Moreover, the ECT group exhibited greater improvements in quality of life and cognitive function. The study also revealed that the ECT group had lower variations in the levels of BDNF and IL-6 compared with the non-ECT group. This suggests that ECT influences neuroplasticity and inflammation, potentially contributing to its therapeutic effects. These findings highlight the superior efficacy and safety of ECT as a treatment option for severe MDD, particularly in cases where traditional therapies fail. This study emphasizes the potential advantages of ECT in mitigating depressive symptoms, improving well-being, and enhancing cognitive capabilities. Furthermore, the exploration of biomarkers provides insights into the mechanisms underlying the effects of ECT and opens avenues for future research on personalized treatment approaches. Despite these positive outcomes, further investigations are required to address certain unresolved questions. Future studies should focus on the long-term effects, potential mechanisms of action, and comparisons between ECT and emerging treatment modalities. Further research is necessary to optimize therapeutic approaches, address stigmatization, and improve outcomes in patients with treatment-resistant MDD.

Research conclusions

The conclusions of this study indicate that ECT is a potentially advantageous therapeutic approach for individuals with severe MDD who do not respond to traditional treatments. This study found that ECT is safer and more potent than medication and/or therapy in mitigating depressive symptoms, enhancing well-being, and bolstering cognitive capabilities. This study also demonstrated that ECT may influence the levels of BDNF and the cytokine IL-6, indicators of neuroplasticity and inflammation, respectively. This study provides new evidence for the efficacy and safety of ECT as a treatment option for severe MDD and challenges the misconceptions and stigma surrounding this alternative therapy. These findings have implications for the development of new therapeutic approaches for MDD and underscore the need for further research in this area.

Research perspectives

Future studies in this field should focus on several aspects. First, further investigations are needed to examine the long-term effects of ECT on depressive symptoms, quality of life, and cognitive function in individuals with MDD. Longitudinal studies can provide valuable insights into the durability of the effects of ECT and its potential as maintenance therapy. Additionally, future research should explore the underlying mechanisms of ECT, particularly its influence on neuroplasticity and inflammatory markers such as BDNF and IL-6. Understanding these mechanisms could guide the development of targeted interventions and improve treatment outcomes. Moreover, studies should be conducted to directly compare ECT with other emerging treatments, such as transcranial magnetic stimulation or ketamine infusion therapy, to determine the most effective and personalized treatment options for different subgroups of patients with MDD. These research perspectives can contribute to advancing the field and optimizing therapeutic approaches for patients with severe MDD.

FOOTNOTES

Author contributions: Han KY, Wang CM, and Lv LZ were responsible for the study conception and design; Du CB and Qiao J provided administrative support; Han KY and Lv LZ provided the study materials and patients; Wang YL and Qiao J conducted data collection; Han KY and Lv LZ conducted data analysis and interpretation; All authors contributed to the manuscript writing process and granted final approval for the manuscript.

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Effectiveness of menstruation hygiene skills training for adolescents with autism

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Abstract

BACKGROUND

Adolescents with autism spectrum disorder (ASD) may encounter many difficulties with their menstrual cycles. Potential challenges that adolescents with ASD may face include understanding physical changes, coping with symptoms, emotional sensitivity, communication, personal care, and hygiene.

AIM

To evaluate the effect of menstrual hygiene skills training given to adolescents with ASD on their menstrual hygiene skills.

METHODS

The study was conducted with 15 adolescents diagnosed with ASD by the single group pre-test and post-test model in three special education centers in Türkiye. Data were collected with the Adolescent and Parent Information Form and the Adolescent-Specific Menstrual Hygiene Skill Registration Form.

RESULTS

While the mean age of adolescents was 16.06 ± 0.88 years, the mean age of individuals responsible for adolescent care was 43.66 ± 5.56 years. While 60.0% of the adolescents noticed the onset of bleeding before training, this rate was 93.3% after training. The Adolescent-Specific Menstrual Hygiene Skill Registration Form showed a statistically significant increase in the application steps after the training. The difference between the menstrual hygiene skill scores of adolescents

diagnosed with ASD before and after training was significant.

CONCLUSION

The menstrual hygiene skills training given to adolescents with ASD was beneficial in increasing their menstrual hygiene skills. These individuals must take responsibility during menstruation and independently manage their continuous care activities.

Key Words: Autism; Adolescent; Menstruation; Hygiene; Training

Core Tip: Adolescents with autism spectrum disorder (ASD) may encounter many difficulties with their menstrual cycles. This study with 15 adolescents diagnosed with ASD by the single group pre-test and post-test model in three special education centers in Türkiye aimed to evaluate the effect of menstrual hygiene skills training given to adolescents with ASD on their menstrual hygiene skills. The menstrual hygiene skills training given to adolescents with ASD was beneficial in increasing their menstrual hygiene skills. These individuals must take responsibility during menstruation and independently manage their continuous care activities.

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INTRODUCTION

Adolescence is a transitional stage of development between childhood and adulthood. It is characterized by rapid physical, cognitive, emotional, and social changes. Most healthy adolescents adapt to this physical and psychosocial developmental process[1]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition definition, autism spectrum disorder (ASD) is a pervasive developmental disorder characterized by disorders in social interaction and communication and limited and repetitive behaviors, and causes limitations in the individual's daily life functions with its early symptoms[2]. The challenges faced by adolescents with ASD are multifaceted and can vary from person to person. Some difficulties faced by adolescents diagnosed with ASD are social difficulties, communication challenges, restricted and repetitive behaviors, sensory sensitivities, transitioning to adulthood, and mental health concerns. The transition to puberty can be particularly challenging for individuals with ASD. However, many of the challenges and experiences faced by individuals with ASD can be changed. Supportive interventions, individualized strategies, and a multidisciplinary approach can significantly help address these challenges and promote the well-being and development of adolescents with ASD[1,3,4].

Adolescents with ASD may encounter many difficulties with their menstrual cycles. Potential challenges that adolescents with ASD may face include understanding physical changes, coping with symptoms, emotional sensitivity, communication, personal care, and hygiene. They may have difficulty dealing with newly emerging situations such as foul odor, blood flow situation/feeling, and using sanitary pads, especially during menstruation[5]. If these changes are not adequately explained to adolescents with ASD, periodic crises and coping problems may occur. Even a simple skill like changing menstrual pads can become a complex motor skill for them[6]. It is essential to approach these challenges with sensitivity, individualized support, and an understanding of the specific needs and abilities of each adolescent with ASD. Collaborating with healthcare providers, educators, and caregivers can help create tailored strategies to address these challenges effectively[3,5,7,8].

A limited number of studies were found in the literature on menstruation periods in individuals with autism. One of these studies was conducted with two mentally disabled individuals[7]. There has been no study with a well-explained methodology and sufficient sample size that evaluates the effectiveness of training on menstrual hygiene skills with only a single focus group, such as adolescents with ASD. This study was planned to evaluate the effect of menstruation hygiene skill training given to adolescents with ASD on the ability to change and wear menstrual pads.

Research hypotheses

H_1: The menstrual hygiene skill level of the adolescent with ASD who is given menstrual hygiene skill training increases.

H_2: Menstrual hygiene skills training increases the independence of adolescents.

MATERIALS AND METHODS

Research design

This study was conducted in three special education centers in the provinces of Istanbul and Muğla between April 2022 and February 2023, using the "Single Group Pre-Test and Post-Test Model," which is one of the semi-experimental study methods. Creswell[9] sees the preference for single-group experimental design as necessary for the nature of the research in studies where a new training module is developed and applied.

Setting, participants, and recruitment

In calculating the sample size, studies compatible with the purpose and design of the research were examined. There is no research in the literature on the menstrual hygiene skill requirements of adolescents with ASD. Therefore, the research of Gölbaşi *et al*[10] on the effectiveness of peer education on menstrual hygiene with healthy adolescents was the basis for calculating the sample. According to this research, Menstrual Health Behaviors change was used in calculating the sample. When an increase of 5.69 points in the mean Menstrual Health Behaviors score was considered significant, the minimum sample size to be reached was 15. Since only the positive change in menstrual hygiene behavior was taken as the basis in our study, the sample size for this study was calculated as 15 adolescents with ASD using the G-Power software program with a margin of error of 0.05 and 80% power.

For this research, permission to conduct the study was requested from all special education units affiliated with the National Education in Istanbul and Muğla. However, only two private education institutions in Istanbul and one private education institution in Muğla granted permission for the research. The study was conducted in three centers affiliated with national education that had granted permission.

A total of 26 females with ASD were present across the participating institutions. Six females were excluded from the study: three females diagnosed with severe autism according to the Gilliam Autism Rating Scale-2 (GARS-2) score; and three females who were older than 18 years of age. Considering the data loss in the specified date range, 20 participants were invited to the research. Sample selection was not made. Three adolescents/parents did not volunteer to participate in the study, and two participants did not perform the post-test. As a result, 15 adolescents diagnosed with ASD were included in the study.

Inclusion criteria for the study were that the adolescent was diagnosed with ASD, the adult responsible for the adolescent's care was older than 18 years, and the adolescent was between the ages of 9-18 years (determined by considering the beginning of the menstrual cycle and the age of enrollment in special education centers), the adolescent's menstrual cycle started, the adolescent's hand washing skills, the adolescent's ability to fulfill instructions that require a single action, the adolescent's ability to watch visual stimuli such as projection shows, video viewing, *etc*, the adolescent's ability to perform the movements shown, the GARS-2 score as "mild" and "moderate," and the adolescent and the adult responsible for her care did not have hearing and visual impairment.

Data collection

Menstruation hygiene skills training: The training was a menstrual hygiene skill training in which visual methods and resuscitation methods were used to teach menstrual hygiene skills to adolescents with ASD. The training was given to the adolescents for half an hour 3 d a week. In each training group, two adolescents with ASD with similar characteristics and a teacher participated. Based on GARS-2 scores, adolescents with moderate autism were placed in one training group, while those with mild autism were placed in another training group. All training was completed in the same group, with the same teacher and researcher. The same researcher and a special education teacher gave the training in each training interview to standardize education. The training frequency, duration, and the number of participants were prepared with the recommendation of a pedagogue/psychologist so that adolescents could best understand and reinforce the skill. In addition, the researchers attended a seminar titled "Autism and Sexuality." For the visual method, a presentation consisting of only pictures prepared by the researchers was used. A pedagogue and special education teacher checked the suitability of the pictures in the presentation. A doll the size of an adolescent was used in the demonstration. With the help of this doll, the menstrual pad change skill was explained practically, and the adolescents were asked to repeat this skill (Table 1).

In addition to the training given to adolescents with ASD, video-assisted "Menstrual Hygiene Training: For Adults" was shown to the adults responsible for their care. Thus, individual differences in menstrual hygiene habits were minimized.

Procedure

Data were collected with the Adolescent and Parent Information Form and Adolescent-Specific Menstrual Hygiene Skill Registration Form, which the researchers created in line with the literature. First, training groups consisting of two participants with common characteristics were determined according to the adolescent's score and learning ability from the GARS-2. While determining the training groups, a consultation was received from the expert pedagogue and special education teacher. The pre-test and post-test of the study were performed by the individual responsible for the care of the adolescent. The aim of the research and how to use the data collection tools were explained to the individuals responsible for the care of the adolescents included in the study. A training video on menstrual hygiene was watched and then sent to the individual for viewing. In the first interview, the Adolescent and Parent Information Form and the Adolescent-Specific Menstrual Hygiene Skill Registration Form were administered to the participants included in the study through the individual responsible. In the post-test, only the Menstrual Hygiene Skills Registration Form was used. The individuals responsible for the care of the adolescents completed the post-test at home during the adolescent's first

Table 1 Application steps of changing sanitary pads

No	Steps
1	She noticed that she had started bleeding
2	She informed me about it
3	She either took off her clothes on her own or I helped her
4	She either removed her underwear on her own or I assisted her
5	She washed her hands
6	She retrieved a fresh pair of underwear
7	She opened the bag and took out a sanitary pad
8	She placed the sanitary pad onto her underwear without touching it directly, either by herself or with my assistance
9	She put on her underwear, either independently or with my help
10	She put on her pants, either by herself or with my assistance
11	She washed her hands and dried them using a towel
12	She realized that she needed to change her pad when the menstrual pad was dirty
13	She successfully removed the soiled pad
14	She either independently wrapped the dirty pad in her bag or I assisted her in doing so
15	She disposed of the dirty pad in the trash
16	She used toilet paper to wipe her perineum from front to back and discarded the used toilet paper in the trash
17	She took the clean, sanitary pad out of its bag and positioned it in her underwear
18	She put on her underwear and pants, either on her own or with my assistance
19	She washed her hands

menstrual cycle after training.

Data collection tools

Adolescent and parent information form: This form, which the researchers prepared, consisted of 11 questions to evaluate the sociodemographic characteristics of adolescents and parents, such as age, education status, income status, and menstrual pattern of adolescents (how many days they have menstrual bleeding and duration). The researchers filled this form with the face-to-face interview technique with the individuals responsible for the care of the adolescents.

GARS-2: The scale was used to determine inclusion criteria and training groups. The Turkish adaptation and validity and reliability studies of the scale were performed by Diken *et al*[11]. GARS-2 is a rating scale that aims to evaluate individuals aged 3–23 years who exhibit behaviors that characterize the autistic disorder. The GARS-2 is a Likert-type scale scored with an opinion-based four-point rating. GARS-2 consists of three subscales: stereotypical behaviors; communication; and social interaction. The scale consists of 42 items in total, with 14 items in each subscale. The highest score that can be obtained from the scale is 153, while the lowest score is 55. A high score indicates a high level of autistic disorder, while a low score indicates a low level of autistic disorder[11].

Adolescent-specific menstrual hygiene skill registration form: This form was created by researchers in parallel with Menstrual Hygiene Skills Training. This form was developed since no scale or form evaluates menstrual hygiene skills in the literature. Expert opinions from 10 individuals (academics in women's health and gynecologic nursing and pediatric nursing, psychologist, pedagogue, and special education teacher) were taken in developing and creating the form. The applicability and comprehensibility of the form were evaluated in a pilot study with five adolescent caregivers before the research data was collected. Incomprehensible items were renewed again. The adolescent was expected to complete 19 skill items in the form. Next to each skill item were "applied" and "not applied" options. In the form, "applied" was scored as 1 point and "did not apply" as 0 points. This scoring compared the pre-test and post-test. A minimum of 0 and a maximum of 19 points were taken.

Statistical analysis

Data were analyzed using the SPSS Statistics program (version 22; IBM Corp., Armonk, NY, United States). Descriptive statistics, mean, and standard deviation were used for continuous variables. Categorical variables were calculated as numbers and percentages. The normality of the distribution of the data was evaluated with the Shapiro-Wilks test, and it was found that the data were not normally distributed. Data were calculated as numbers and percentages before and after training and analyzed using the Wilcoxon signed-rank test. A statistical significance value of $P < 0.05$ was adopted.

Table 2 Descriptive characteristics of the adolescents

Descriptive characteristics	mean ± SD	Min-max
Age in yr	16.06 ± 0.88	15-17
Parent's age in yr	43.66 ± 5.56	36-52
Age of menarche	13.73 ± 1.09	11-15
Menstruation frequency in d	38.60 ± 39.25	21-180
Period of menstruation in d	5.13 ± 0.99	4-7
	n	%
Is the menstrual cycle regular?		
Yes	13	86.7
No	2	13.3
Adult caregiver		
Mother	14	93.3
Other	1	6.7
Adult education level		
Literate	1	6.7
Primary education	6	40.0
High school	8	53.3

SD: Standard deviation.

RESULTS

While the mean age of adolescents was 16.06 ± 0.88 years, the mean age of adults responsible for adolescent care was 43.66 ± 5.56 years. The mean age of menarche in adolescents was 13.73 ± 1.09 years, the frequency of menstruation was every 38.60 ± 39.25 d, the mean duration of menstruation was 5.13 ± 0.99 d, and the menstrual cycle of 86.7% of the adolescents was regular. The mothers of 93.3% of the adolescents were responsible for their care, and 53.3% of the adults were high school graduates (Table 2).

Table 3 shows the distribution of adolescents' menstrual hygiene skills before and after the training. While 60.0% of the adolescents noticed the onset of bleeding before the training, this rate was 93.3% after the training. Informing the adult about the application steps (80.0%), removing clothes/getting help (60.0%), removing underwear/getting help (66.7%), washing hands (73.3%), receiving clean underwear (66.7%), and removing the sanitary pad out of its bag (60.0%) reached 100% after the training. While the rate of placing the sanitary pad in underwear without touching anything or doing it with help was 60.0% before the training, it was 93.3% after the training. The steps of putting on underwear/getting help (60.0%), putting on pants/getting help (73.3%), and washing hands and drying with a towel (73.3%) reached 100% after the training. Before the training, 66.7% of the adolescents understood that the pad should be changed when it gets soil, while 73.3% understood it after the training. Being able to remove the soiled pad (60.0%), wrap the soiled pad in a bag or do it with help (66.7%), throw it in the trash (66.7%), wipe the perineum from front to back with toilet paper, throw the toilet paper in the trash (60.0%), removing the sanitary pad from its bag and placing it in the underwear (60.0%), putting on the underwear and trousers or doing it with help (86.7%), and washing hands (93.3%) reached 100%. The differences in the following steps of the menstrual hygiene training given to adolescents with ASD were statistically significant before and after the training: took off her clothes/did it with help (P = 0.014); took off her underwear/did it with help (P = 0.025); washed her hands (P = 0.046); took clean underwear (P = 0.025); took the menstrual pad and took it out of its bag (P = 0.014); put on the underwear/did it with help (P = 0.014); put on the pants/do it with help (P = 0.046); washed her hands and dried them with a towel (P = 0.046); took out the dirty pad (P = 0.014); wrapped the soiled pad in her bag/did it with help (P = 0.025); threw the pad in the trash (P = 0.025); wiped her perineum with toilet paper from front to back and threw the toilet paper in the trash (P = 0.014); and removed the sanitary pad out of its bag and placed it in her underwear (P = 0.014) (Table 3).

The difference between the menstrual hygiene skill scores of adolescents diagnosed with ASD before and after training was statistically significant (P < 0.005) (Table 4).

Table 3 Distribution of adolescents' menstrual hygiene skills before and after training

Application steps	Before training				After training			
	Applied		Not applied		Applied		Not applied	
	n	%	*n*	%	*n*	%	*n*	%
She noticed that she had started bleeding	9	60.0	6	40.0	14	93.3	1	6.7
She informed me about it	12	80.0	3	20.0	15	100	-	-
She either took off her clothes on her own or I helped her	9	60.0	6	40.0	15	100	-	-
She either removed her underwear on her own or I assisted her	10	66.7	5	33.3	15	100	-	-
She washed her hands	11	73.3	4	26.7	15	100	-	-
She retrieved a fresh pair of underwear	10	66.7	5	33.3	15	100	-	-
She opened the bag and took out a sanitary pad	9	60.0	6	40.0	15	100	-	-
She placed the sanitary pad onto her underwear without touching it directly, either by herself or with my assistance	9	60.0	6	40.0	14	93.3	1	6.7
She put on her underwear, either independently or with my help	9	60.0	6	40.0	15	100	-	-
She put on her pants, either by herself or with my assistance	11	73.3	4	26.7	15	100	-	-
She washed her hands and dried them using a towel	11	73.3	4	26.7	15	100	-	-
She realized that she needed to change her pad	10	66.7	5	33.3	11	73.3	4	26.7
When the menstrual pad was dirty								
She successfully removed the soiled pad	9	60.0	6	40.0	15	100	-	-
She either independently wrapped the dirty pad in her bag or I assisted her in doing so	10	66.7	5	33.3	15	100	-	-
She disposed of the dirty pad in the trash	10	66.7	5	33.3	15	100	-	-
She used toilet paper to wipe her perineum from front to back and discarded the used toilet paper in the trash	9	60.0	6	40.0	15	100	-	-
She took the clean sanitary pad out of its bag and positioned it in her underwear	9	60.0	6	40.0	15	100	-	-
She put on her underwear and pants, either on her own or with my assistance	13	86.7	2	13.3	15	100	-	-
She washed her hands	14	93.3	1	6.7	15	100	-	-

Table 4 Menstrual hygiene skills analysis and average scores of adolescents before and after training

Before training, mean ± SD (min-max)	After training, mean ± SD (min-max)	*P* (test value)
12.93 ± 5.52 (2-19)	18.60 ± 0.73 (17-19)	0.002 (-3.065)

SD: Standard deviation.

DISCUSSION

In this study, menstruation hygiene skill training was given to adolescents with ASD, video-based menstruation hygiene training was given to the individuals responsible for their care, and the hygiene skills of adolescents with ASD were revealed for the first time. The menstruation process in ASD-diagnosed adolescents was the same as in their healthy peers. These young people may have difficulty coping with emerging situations such as foul odor, blood flow situations/feelings, and using menstrual pads during menstruation. If ASD-diagnosed adolescents are not educated about these changes, periodic crises and coping problems can be seen in adolescents. When we look at the literature, the importance of training young people and their parents about the menstruation process is emphasized. However, young people with ASD remain in the background of this training process.

In many societies, the general viewpoint towards adolescents with ASD may cause the problems, especially during the menstrual period, to be ignored. Menstruation management of adolescents with ASD is complex and requires great patience. Menstruation hygiene skills are one of the biggest problems of adolescents with ASD and their caregivers. Communicating with adolescents with ASD is very important in terms of menstruation management. These young people face many complications during the menstruation process. In order to manage this process in the best way, adolescents and their caregivers should be taught to explain menstruation, physical changes, and especially hygiene

skills. One of the hygiene skills is noticing the start of menstrual bleeding. The current study applied menstrual hygiene skill training to adolescents with ASD. Most adolescents (93.3%) noticed the onset of menstrual bleeding after the training. In addition, all of the adolescents informed their caregivers that menstrual bleeding occurred after the training. In addition to the limited number of studies on this subject in the literature, the current study was consistent with the cross-sectional study of Rodgers *et al*[12] and the mixed-method study of adolescents with mental retardation[12,13].

Adolescents with ASD must be able to perform their daily routine and self-care skills to exist in society and continue their lives like healthy adolescents. For adolescents with ASD to continue their daily routines effectively in their communities, they must first have the ability to provide self-care and general hygiene and be able to dress independently. In particular, they should be able to change menstrual pads independently, which is an important aspect of self-care and menstruation management. Adolescents with ASD should be trained to develop skills and behaviors to acquire self-care skills. In the current study, it was observed that after the menstrual hygiene skill training, all of the adolescents took off their clothes and underwear by themselves or got help and were able to remove the menstrual pad from the bag before changing the menstrual pad. In addition, all the adolescents took out the soiled pad, wrapped it in their bags, and disposed of it properly after the training. In addition, after the training, it was determined that all adolescents with ASD completed the perineum cleaning properly by wiping their perineum with toilet paper from front to back. Another striking study result was that all participants washed their hands before and after changing the soiled pads after the training. In addition, while 60.0% of the adolescents could take the clean menstrual pad out of its bag and place it in their underwear before the training, it was observed that this rate was 100% after the training. According to the study results, adolescents' menstrual hygiene skill analysis scores before and after training increased significantly. In another practical study on dolls in Türkiye, pad-changing training was given to mentally retarded adolescents. It was observed that the training increased the pad-changing skills of adolescents[8]. In addition, the study results aligned with the limited study emphasizing the importance of menstruation training given to adolescents with special needs[14-17]. Further research must reveal the positive results of menstrual hygiene skills training given to adolescents with ASD.

CONCLUSION

In this study, menstruation hygiene skill training was given to adolescents diagnosed with ASD, and the effect of this training on the menstrual hygiene behavior of adolescents was evaluated. As a result of the study, it was observed that the self-care skills, such as hand washing and perineal cleaning especially in changing hygienic pads, of adolescents diagnosed with ASD increased after the training. With the successful results of this study, the importance of dividing the menstruation hygiene skill training into more than one step in adolescents with ASD and conducting this training in small groups became evident. Future research should focus on identifying developmentally sensitive pathways to reveal the voices of adolescents with ASD on their menstruation and puberty experiences. In addition, this study was one of the rare studies that increased the menstrual hygiene skills of adolescents with ASD by training groups of two participants with visual methods and demonstration methods.

Limitations

The present study had some limitations, and future researchers may consider addressing these as they explore this topic. First, this study focused only on ASD adolescents enrolled in special education centers. On the other hand, some adolescents diagnosed with ASD may be unable to access special education centers and face different difficulties. In addition, since the research data were collected from the people responsible for the care of adolescents with ASD, the information obtained may lead to positive or negative biases. The other limitation affecting the generalization of these results was the relatively small sample size. Nonetheless, the data obtained will serve as a valuable foundation for guiding future randomized controlled studies with a larger number of patients.

ARTICLE HIGHLIGHTS

Research background

Adolescents with autism spectrum disorder (ASD) may encounter many difficulties with their menstrual cycles. Potential challenges that adolescents with ASD may face include understanding physical changes, coping with symptoms, emotional sensitivity, communication, personal care, and hygiene. They may have difficulty dealing with newly emerging situations such as foul odor, blood flow situation/feeling, and using sanitary pads, especially during menstruation.

Research motivation

One of the important problems faced by adolescents with ASD during the menstrual period is to practice menstrual hygiene skills. This study was carried out in order to teach this skill to adolescents with ASD and to support their independence.

Research objectives

This study was planned to evaluate the effect of menstruation hygiene skill training given to adolescents with ASD on the

ability to change and wear menstrual pads.

Research methods

This study was conducted in three special education centers in the provinces of Istanbul and Muğla between April 2022 and February 2023, using the "Single Group Pre-Test and Post-Test Model," which is one of the semi-experimental study methods. Before the training, the Adolescent and Parent Information Form and the Adolescent-Specific Menstrual Hygiene Skill Registration Form were administered to the participants included in the study through the individual responsible. In the post-test, only the Menstrual Hygiene Skills Registration Form was used. The individuals responsible for the care of the adolescents completed the post-test at home during the adolescent's first menstrual cycle after training.

Research results

The mean age of adolescents was 16.06 ± 0.88 years. The mean age of menarche in adolescents was 13.73 ± 1.09 years, the frequency of menstruation was every 38.60 ± 39.25 d, the mean duration of menstruation was 5.13 ± 0.99 d, and the menstrual cycle of 86.7% of the adolescents was regular. The mothers of 93.3% of the adolescents were responsible for their care, and 53.3% of the adults were high school graduates. The difference between the menstrual hygiene skill scores of adolescents diagnosed with ASD before and after training was statistically significant ($P < 0.005$).

Research conclusions

It was observed that the self-care skills, such as hand washing and perineal cleaning especially in changing hygienic pads, of adolescents diagnosed with ASD increased after the training.

Research perspectives

With the successful results of this study, the importance of dividing the menstruation hygiene skill training into more than one step in adolescents with ASD and conducting this training in small groups became evident. In addition, this study was one of the rare studies that increased the menstrual hygiene skills of adolescents with ASD by training groups of two participants with visual methods and demonstration methods.

FOOTNOTES

Author contributions: Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to study design; Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to data collection; Yılmaz B contributed to data analysis; Kaydırak M contributed to study supervision; Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to manuscript writing; Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to critical revisions for important intellectual content; All authors read and approved the final manuscript.

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Institutional review board statement: Approval was obtained from the Muğla Sıtkı Koçman University Health Sciences Ethics Committee for the study (Protocol No. 200179/Decision No. 6). Permission was obtained from the special education centers where the research was conducted. The aim and method of the study were explained and informed to the individuals responsible for the adolescent's care, parents, and special education center staff. The purpose of the study, how the study would be carried out, that they could quickly leave the study whenever they wanted, and that the information received would be kept confidential was explained to the individuals responsible for the adolescent's care. The study was conducted in accordance with the Principles of the Declaration of Helsinki.

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CASE REPORT

Cerebrotendinous xanthomatosis presenting with schizophrenia-like disorder: A case report

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Abstract

BACKGROUND

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid-storage disorder caused by mutations in *CYP27A1*. Psychiatric manifestations in CTX are rare and nonspecific, and they often lead to considerable diagnostic and treatment delay.

CASE SUMMARY

A 33-year-old female patient admitted to the psychiatric ward for presentation of delusions, hallucinations, and behavioral disturbance is reported. The patient presented with cholestasis, cataract, Achilles tendon xanthoma, and cerebellar signs in adulthood and with intellectual disability and learning difficulties in childhood. After the characteristic CTX findings on imaging were obtained, a pathological examination of the Achilles tendon xanthoma was refined. Replacement therapy was then initiated after the diagnosis was clarified by genetic analysis. During hospitalization in the psychiatric ward, the nonspecific psychiatric manifestations of the patient posed difficulty in diagnosis. After the patient's history of CTX was identified, the patient was diagnosed with organic schizophrenia-like disorder, and psychotic symptoms were controlled by replacement therapy combined with antipsychotic medication.

CONCLUSION
Psychiatrists should be aware of CTX, its psychiatric manifestations, and clinical features and avoid misdiagnosis of CTX for timely intervention.

Key Words: Cerebrotendinous xanthomatosis; Psychotic symptom; *CYP27A1* gene mutation; Novel likely pathogenic variant; Case report

Core Tip: Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid-storage disorder, characterized by diverse systemic and neuropsychiatric manifestations. Psychiatric manifestations in CTX are typically nonspecific, and past cases have reported a scarcity of psychotic symptoms, particularly delusions and hallucinations. In this report, we present a case of CTX exhibiting a hallucinatory-paranoid syndrome and describe the diagnostic and therapeutic processes associated with CTX. The long-term treatment effect in CTX may depend on age at start of treatment and psychiatrists should be cognizant of CTX to facilitate timely intervention.

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INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive inherited metabolic lipid-storage disorder related to bile acid biosynthesis pathways. It is caused by biallelic pathogenic variants in *CYP27A1* (2q35), which codes sterol 27-hydroxylase, a mitochondrial enzyme of the cytochrome P450 oxidase system. Reduction in the activity of this enzyme leads to an increased formation and storage of abnormal lipid content in several tissues, especially tendons, lenses, and the peripheral and central nervous systems. Typically, the affected individuals develop tendon xanthomas, cataracts, dementia, pyramidal paresis, cerebellar ataxia, and peripheral neuropathy. As epidemiologic data are limited and CTX may be substantially underdiagnosed, the prevalence of the disease is underestimated. No consensus exists on the prevalence of CTX, with an estimated rate of < 3:100000–5:100000 worldwide[1]. A recent worldwide genetic epidemiological study estimated the incidence of CTX to be 1:36042-1:468624 and highest among South Asians and East Asians, followed by North Americans, Europeans, and Africans[2]. The psychiatric manifestations of CTX are variable, with the most common manifestations being intellectual disability, behavioral disorders, and mood disorders. Few patients have delusions, hallucinations, paranoid ideas, or catatonia, similar to the features of schizophrenia. Thus, making a timely diagnosis is difficult for clinicians. Early diagnosis and treatment initiation in patients with CTX is of great importance because significant reversal of the disease progression could be achieved. Consequently, an enhanced understanding of this rare disease is necessary.

CASE PRESENTATION

Chief complaints

A 33-year-old woman was admitted to the psychiatric acute ward with the following symptoms: delusions of persecution, auditory hallucination, impulsive behavior, and emotional instability.

History of present illness

For 6 mo, the patient showed hostility towards her colleagues, firmly believing that they wanted to harm her. She could hear abusive voices of colleagues when she was alone. The false belief and voice interfered with the social relations and behavior of the patient, leading to outrunning behavior. In addition, the patient exhibited impulsive acts and temperamental behavior, such as tearing people's clothes, smashing things, standing outside naked when she became excited, and running around at midnight. She also experienced severe depression for several days, with crying and expressing a desire to commit suicide by euthanasia.

History of past illness

According to her mother, the patient has been weak and obtuse since childhood and was unable to pass primary school exams. She required supervision and care from her family in her personal life. Despite being able to work, she could not perform her job well and did not get along with her colleagues, leading to her dismissal from several companies. At age

18, she underwent cataract surgery, and at age 26, she underwent cholecystectomy for cholestasis.

A review of the patient's medical records revealed that she presented with swelling in her left Achilles tendon, pain, and skewed walking to the right side 5 years ago. Three years ago, she was admitted to the neurology department, where biochemical tests revealed an elevated total biliary acid level of 11.2 μmol/L (normal value ≤ 10.0) and decreased levels of chenodeoxycholic acid and ursodeoxycholic acid. Subsequently, a biopsy of the left Achilles tendon was performed, revealing numerous lipid crystals and a few foamy macrophages (Figure 1A). The patient underwent genetic analysis, which identified two mutations in the *CYP27A1* gene associated with CTX: c.1263 + 3G>C and c.379C>T. On the basis of these findings, the patient was ultimately diagnosed with CTX and prescribed chenodeoxycholic acid (750 mg/d) and rosuvastatin (10 mg/d).

Personal and family history

There was no family history of psychiatric diseases.

Physical examination

During hospitalization in the psychiatric ward, the patient's brief psychiatric rating sale (BPRS) score was 40, her Wechsler intelligence scale score was 65, and the total biliary acid returned to normal levels. Nervous system examination showed normal muscle tone in the extremities, grade 5 muscle strength, instability in the heel-knee-tibia test of the right lower extremity, and a positive Romberg sign. In the mental status examination, the patient exhibited the following: verbal auditory hallucination; delusions of persecution; negative perceptions; irritability; childish emotions; poor general knowledge, understanding, judgment, and calculation; impulsivity; and lack of insight.

Laboratory examinations

After nearly 3 years of adequate chenodeoxycholic acid treatment, the total biliary acid level returned to normal.

Imaging examinations

Brain magnetic resonance imaging (MRI) revealed symmetrical patchy abnormal signals in the dentate nuclei and deep medulla of the bilateral cerebellar hemispheres. These signals exhibited a slight decrease in signal intensity on T1-weighted images (T1WI) (Figure 2A) and a slight increase in signal intensity on fluid attenuated inversion recovery (FLAIR) (Figure 2B). Left-ankle-joint MRI showed that the inhomogeneous area had a considerable local thickening of the left Achilles tendon. The area displayed clear boundaries measuring approximately 6.6 cm × 1.2 cm and exhibited a slightly elevated signal intensity on T1WI and a similar slightly elevated signal intensity on the proton density weighted image, accompanied by linear hypointensity within (Figure 1B). Brain magnetic resonance spectroscopy (MRS) showed decreases in N-acetylaspartate (NAA) intensities and increases in lactate and lipid signals (Figure 2C and D).

FINAL DIAGNOSIS

In accordance with International Classification of Diseases-10 criteria, the patient received the following diagnoses: Organic schizophrenia-like disorder and CTX.

TREATMENT

Concurrent with chenodeoxycholic acid treatment for the primary condition, we administered olanzapine to manage the patient's psychotic symptoms, and sodium valproate to stabilize mood while augmenting the antipsychotic medication.

OUTCOME AND FOLLOW-UP

After treatment, the psychotic symptoms were remarkably relieved, her emotions were relatively stable, and impulsive or noisy behavior did not manifest itself. The reassessed BPRS score was 21. During the 3-mo outpatient follow-up, the patient took medication on time and occasionally experienced emotional fluctuations but was able to listen to persuasion and did not exhibit any more impulsive behavior or running.

DISCUSSION

The clinical presentation of CTX is characterized by diverse systemic and neuropsychiatric manifestations and combinations of symptoms that vary from patient to patient. Of these, psychiatric disturbances are considered a strong diagnostic indicator of CTX, but the symptoms are so variable, as in this case, that making a timely diagnosis is difficult for clinicians. CTX is estimated to have a 15–20-year diagnostic delay[3,4].

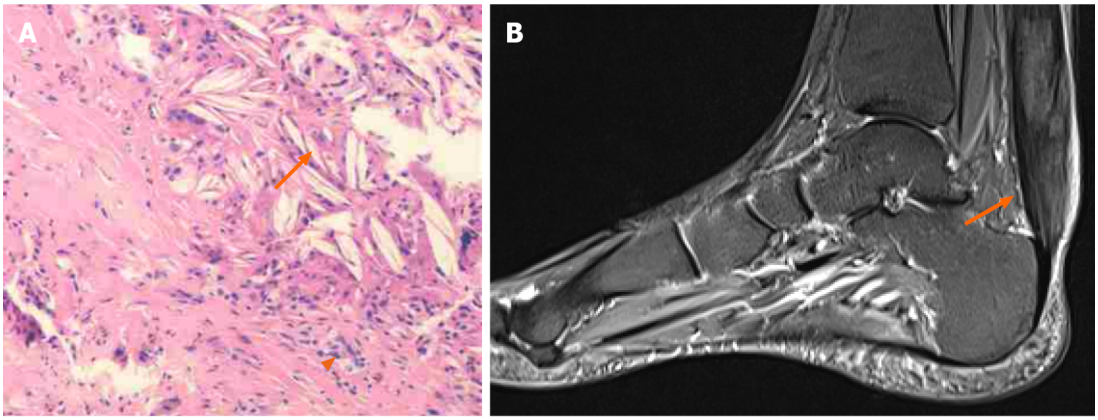

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Figure 1 Imaging of left ankle joint and histopathological analysis of the resected specimen. A: Histological findings of left Achilles tendon xanthoma shows foamy macrophages (arrowheads) and lipid crystal (arrows); B: Left ankle joint magnetic resonance imaging reveals a mild increase in signal intensity on the proton density-weighted image, accompanied by linear hypointensity within.

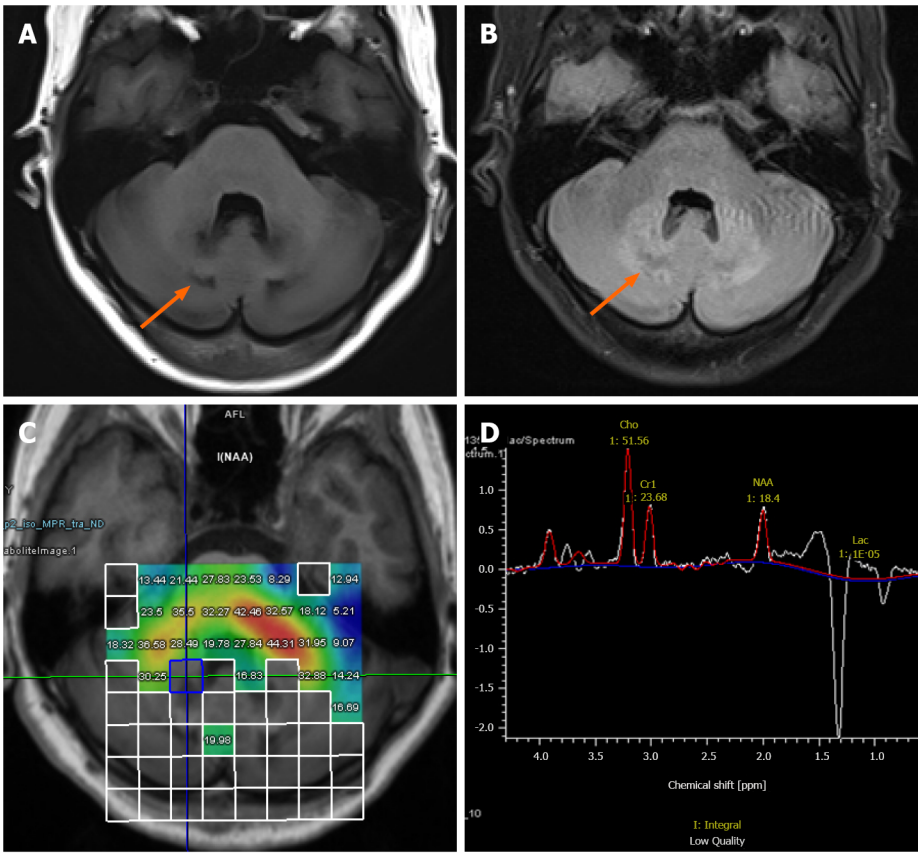

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Figure 2 Brain imaging findings. A: Brain magnetic resonance imaging reveals patchy symmetrical abnormal signals in the dentate nuclei and deep medulla of bilateral cerebellar hemispheres and a slight decrease in signal intensity on T1 weighted image; B: Slight increase in signal intensity on fluid attenuated inversion recovery; C: Magnetic resonance spectroscopy shows right cerebellar dentate nuclei; D: Decreases in N-acetylaspartate intensities and increases in lactate signals and lipid signals.

The lack of specificity of the early clinical symptoms of CTX is the main reason why the disease is difficult to diagnose in a timely manner, and clinicians must often consider the clinical features of multiple systems, biochemical tests, and radiological examination. Among them, the dentate nucleic signal change in MRI is considered a strong diagnostic indicator[3]. The distinctive neuroradiological findings of CTX show symmetrical abnormalities in the bilateral cerebellar dentate nuclei region with a low signal intensity on T1WI and a high signal intensity on T2 weighted image and FLAIR. The brain MRS shows decreases in NAA intensities and increases in lactate signals[5]. The gold standard for diagnosing CTX is the analysis of the *CYP27A1* gene. In the present case, two mutations were confirmed in the *CYP27A1* gene by

genetic sequencing, with c.379C > G being previously reported as pathogenic and considered one of the most frequent mutations in the Chinese population[6]. However, the relationship between the unreported mutation at the c.1263 + 3G > C locus and the CTX disease phenotype must be further explored.

The psychiatric manifestations of CTX among the Chinese population are infrequently discussed, but foreign literature suggests that intellectual disability, attention deficit hyperactivity disorder, and autism spectrum disorder are often present in childhood or adolescence, with mood and impulsive behavioral symptoms becoming more prominent in adulthood[7]. In the present case, the patient exhibited psychiatric manifestations consistent with those in previous studies. A notable detail that the patient also exhibited hallucinatory-paranoid syndrome, which was scant in past cases and is the first description in Asian population[8]. Psychotic manifestations in CTX are rare, especially in younger patients, and they are often misattributed to psychiatric disease. Most of the psychiatric manifestations of CTX appear after xanthomas and neurological symptoms[7], allowing psychiatrists to identify this organic disorder more easily. Chenodeoxycholic acid is currently the first-line treatment for CTX, and its combination with antipsychotic medication may be beneficial for most patients if psychotic symptoms are present[8]. In the present case, the bile acid level returned to normal after nearly 3 years of adequate chenodeoxycholic acid treatment. The psychiatric symptoms remarkably improved after the combination of the antipsychotic olanzapine and the mood stabilizer sodium valproate during hospitalization. Moreover, the condition was stable at the 3-mo follow-up, indicating that such drugs have good efficacy on psychiatric symptoms associated with CTX.

The long-term treatment effect in CTX may depend on the age at start of treatment. At a point in time demarcation, two different therapeutic effects were observed. A study showed that patients with CTX who started chenodeoxycholic acid treatment before the age of 24 have a better prognosis[9], whereas a follow-up revealed minimal progression in MRI imaging compared with baseline[10].

CONCLUSION

In psychiatric clinical practice, patients with intellectual disability come to the clinic because of concomitant psychiatric behavioral symptoms, and psychiatric specialists need to pay attention to the differential diagnosis, especially when patients are found to have Achilles tendon xanthomas, juvenile cataracts, childhood-onset chronic diarrhea, and cholestasis. Thus, further improvement of biochemical tests, such as serum cholestanol, radiological examination of the Achilles tendons and brain, and genetic analysis, is needed to avoid a missed or misdiagnosis of CTX for timely intervention.

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FOOTNOTES

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